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THE USE OF INTRAVENOUS ETHYL ALCOHOL IN THE TREATMENT OF STATUS ASTHMATICUS

ETHAN ALLAN BROWN, M.D., F.A.C.A.
Boston, Massachusetts

THE patient who has been wheezing for some hours is hungry, thirsty, tense, and tired. The dehydration and low blood sugar are remedied by intravenous glucose-saline and the tension, by sedation which, encouraging relaxation and sleep, relieves the fatigue. The antispasmodic drugs ameliorate the bronchial spasm. When epinephrine is used, the side reactions include weakness and peripheral vasoconstriction as evidenced by pallor. With aminophyllin, adverse reactions include cerebral throbbing, nausea, and vomiting, accompanied by peripheral vasodilatation as evidenced by flushing and perspiration. The sedatives recommended are frequently spasmogenic and usually respiratory depressants. In any case, it is necessary to use several types of medication, the action of which is not always consistent.

For intravenous treatment, the ideal drug, allowing for the glucose-saline in which it is administered, should be nontoxic, nonallergenic, and evenly and rapidly metabolized, so that its administration may be controlled. There should be a wide margin of safety between the pharmacologic and toxic doses. The drug should be sedative, vasodilating, and, if possible, stimulating to respiration. Ethyl alcohol, given intravenously, fulfills these and other essential criteria.

The oxidation of ethyl alcohol given intravenously is rapidly completed. Of its end products, oxygen and carbon dioxide, the latter, passing off in the lungs, acts as a respiratory stimulant. The calories are easily assimilated and immediately available, 50 c.c. of 95 per cent alcohol representing 600 calories. The sedative action can be quickened or slowed by the rate of intravenous flow. The dilatation of peripheral vessels permits the body to absorb epinephrine from any of the subcutaneous depots, due to previous injection. Additional epinephrine, in doses up to 1.0 c.c., can be added to the intravenous solution.

The pharmacology of ethyl alcohol is not complex. The toxic dose is 7.7 c.c. for each kilogram of the patient's body weight. The dose for analgesia and sleep varies from 1.5 to 3 c.c. per kilogram. Since the average dose for complete narcosis, permitting surgical interference, is 2 to 2.5 c.c. per kilogram, the margin of safety is immediately apparent.[2]

For the narcosis of a patient who weighs 60 kg., 120 c.c. of 95 per cent alcohol and 240 c.c. of 5 per cent glucose-saline is needed. Of this solution, 40 to 60 c.c. causes sleep which, in the majority of patients, is refreshing and marked by contracted pupils and even, steady respiration, the patient awakening in two to five hours. An occasional subject, to whom the solution has been given too rapidly or in too large a quantity, may be irrational for a slight period of time. Behan,[1] who studied thirty patients in whom intravenous ethyl alcohol had been used for the control of postoperative pain, states that 6 per cent had vomiting, transitory headache, and occasional, very slight hematuria. In the present series, since the doses given were much smaller, no ill effects were noted.

Just as the history of alcohol taken orally for preoperative or postoperative pain is long, the history of the use of alcohol intravenously for the same purpose is brief. Goodman and Gilman (Macmillan, 1941) give it no mention. In 1945, Verkhovskaya[3] reported on thirty patients, for whom it had been used for preoperative anesthesia in bone surgery. In this country, Behan[1] used intravenous ethyl alcohol as a postoperative sedative drug in thirty patients, in only five of whom the pain persisted to a degree requiring morphine.

For the present series, 50 c.c. of 95 per cent ethyl alcohol was added to 1,000 c.c. of 5 per cent glucose-saline. If the material is to be prepared by the physician, it is advisable to Seitz-filter the alcohol previous to use. Commercial solutions, containing 5 per cent of ethyl alcohol in glucose-saline, are available with or without added Vitamin B complex. For each patient, the initial intravenous flow was sufficiently rapid to give 100 c.c. within ten minutes, and thereafter permitted to flow from 70 to 100 drops per minute. In one of our patients, in whom the rate was less than 70 drops per minute, there was no response. In all, the intravenous injection was used twenty-five times on six patients, two of whom were hospitalized on two separate occasions.

The first patient studied had suffered from severe bronchial asthma for some years, his attacks of status asthmaticus requiring hospitalization three to four times yearly, each episode lasting from three to six weeks. He responded poorly, if at all, to subcutaneous epinephrine or to ephedrine, aminophyllin, or sedatives taken orally. His response to intravenous aminophyllin (0.5 gm.), in either glucose or sucrose with epinephrine, was variable, and usually poor. Treatment with ethyl alcohol, 0.5 per cent, given by clysis was ineffective, as was a second attempt with a 0.5 per cent ethyl alcohol solution given intravenously. The third solution, containing 5 per cent ethyl alcohol, given at 90 to 100 drops per min-

ute, caused bronchial dilatation within thirty minutes. The patient fell asleep for about fifteen minutes, after which he awakened easily, dozing comfortably over the three-hour period during which the injection was given. The effects on the patient's appearance, respiration, and mental attitude were immediately apparent. With intravenous aminophyllin and other types of drugs, the patient may be much more comfortable, although physical examination of the chest proves the bronchioles to be in a state of spasm. In this patient, the lungs were completely clear of physical signs of bronchial asthma in three hours. The relief lasted twelve hours, after which epinephrine gave no relief, indicating further intravenous injection of the same solution. In all, the patient received four injections and was discharged free of asthma, his remission lasting four weeks. During hospitalization on a second occasion, a 5 per cent solution of ethyl alcohol in glucose-saline again proved efficacious for a severe attack, the symptom-free period lasting twelve hours.

The second patient was admitted in severe status asthmaticus and did not respond to epinephrine by injection or to ephedrine and other drugs taken orally. The patient was in extreme spasm, with cyanotic lips, fingers, and toes. In the past, he had responded to intravenous aminophyllin. A 5 per cent ethyl alcohol solution in glucose-saline was used, and within thirty minutes, the cyanosis was replaced by a warm, normally dry, normally pink flush and sound sleep, associated with a drop in the minute respiratory rate from 40 to 27.

Two successive intravenous injections on the two succeeding days had similar results, the patient being discharged symptom-free. Inquiries showed him to be free of symptoms for the succeeding six weeks.

The remaining patients required from three to five intravenous injections, the response being similar in each. In one patient, the solution given slowly had no effect and aminophyllin was effectively substituted. In another, upon a second admission two weeks following the first, the solution was without effect when given at the rate of 70 to 80 drops per minute, but effective within fifteen minutes when the rate was increased to 100 to 110 drops per minute. The patient, who went to the hospital in severe status asthmaticus, was able to walk home four hours following his admission.

In summary, a 5 per cent ethyl alcohol solution in physiologic 5 per cent glucose-saline, with or without epinephrine 1:1,000 (0.3-1.0 c.c.), given intravenously at the rate of 80 to 100 drops per minute, effectively relieved severe bronchial asthma in five of six patients, who did not respond to the usual medications given by the oral, subcutaneous, and intravenous methods. Two of the patients responded similarly on two successive hospital admissions. No ill effects were anticipated or observed.

The remaining data and the detailed protocols will be part of a subse-

(Continued on Page 273)

CONTINUOUS INTRAVENOUS AMINOPHYLLIN THERAPY IN STATUS ASTHMATICUS

LT. ROBERT J. GOODALL, MC, AUS, and LEON UNGER, M.D., F.A.C.A.
Chicago, Illinois

IN some patients with status asthmaticus symptoms continue despite various accepted methods of treatment. Wheezing, dyspnea, cough and orthopnea persist, and, in addition, loss of strength, weight and morale may also occur. It is with this type of patient that we are here concerned.

Efron[3] first mentioned the use of aminophyllin in asthma, but Herrmann and Aynesworth[4] popularized its use. In 1937 they reported favorable results in status asthmaticus by intravenous injections of 0.25 to 0.5 gm. aminophyllin dissolved in physiological saline solution. Their excellent results have been verified by numerous investigators, including one of us (L. U.[7]). The drug is also useful when given in rectal suppositories, as introduced by Dees,[2] or when instilled in the rectum (10 grains of aminophyllin with 20 c.c. tap water), as suggested by Barach.[1] We have found the oral use of this drug rather ineffective, and nausea frequently occurs.

It is therefore a well-established fact that the intravenous administration of aminophyllin gives more or less quick relief to most asthmatic patients, including some with status asthmaticus. The drug probably relaxes bronchial muscles and allows more air to pass through, as shown by Young and Gilbert,[8] Sollman and Gilbert,[6] and others.

The intermittent intravenous and rectal administration of aminophyllin is standard procedure at Wesley Memorial Hospital. On admission in a severe attack the asthmatic patient usually receives an intravenous injection of 0.25 gm. (3¾ grains) dissolved in 10 c.c. diluent, given slowly through a 10 c.c. syringe. He is then given 0.5 gm. (7½ grains) intravenously, dissolved in 1,000 c.c. of 5 per cent glucose, over a period of three to four hours. This liter infusion is repeated daily for three or four days if necessary. The rectal suppositories or solution are usually given at night. In addition, in severe cases, another 10 c.c. (3¾ grains) are often injected intravenously at night. Epinephrine is avoided in patients with tachycardia, restlessness or pallor. Morphine is never used.

The above regime is open to criticism because:

1. The patient may need four or even more injections of aminophyllin in twenty-four hours.

Read at the meeting of the American College of Allergists, San Francisco, California, June 28 to 30, 1946.

Dr. Goodall was formerly an intern at Wesley Memorial Hospital, Chicago, Illinois.

Dr. Unger is Attending Physician at Wesley Memorial and Cook County Hospitals, Chicago, Illinois.

The aminophyllin used was furnished through courtesy of G. D. Searle Co., Chicago, Illinois.

The authors are grateful to Dr. Andrew de Roetth, also of Wesley Memorial Hospital, and several other interns, for invaluable assistance in carrying out the procedure.

TABLE I. CONTINUOUS INTRAVENOUS AMINOPHYLLIN THERAPY IN STATUS ASTHMATICUS

INDICATIONS. Hospitalized patients in whom previous measures, including intermittent injections of aminophyllin, have failed.
AMOUNT OF AMINOPHYLLIN PER LITER:
(a) 1.0 to 1.5 grams, depending upon severity of symptoms.
(b) Gradually reduced as symptoms decrease.
VEHICLE USED: First, 5 per cent glucose in distilled water. Second liter, 0.9 per cent saline in distilled water, then alternate.
RATE OF FLOW: 28 drops per minute—
1 liter in twelve hours.
2 liters in twenty-four hours.
EQUIPMENT:
(a) 23 gauge, short bevel, 1½ inch needle.
(b) Aminophyllin, 0.50 grams in 20 c.c. or 2.0 c.c. ampules.
(c) Rubber tubing with clamp.
(d) Liter flasks.
(e) Adhesive strips.
SITE OF INJECTION:
Broad volar or dorsal surface of forearm, avoiding joints.
PRECAUTIONS:
(a) Flask must not run dry.
(b) If vein becomes inflamed, transfer to another vein.
TOXIC EFFECTS: None observed.
DURATION OF TREATMENT: Average 7-14 days.
RESULTS: Good to excellent in most cases. Relaxation usually occurs. Reduces need for other methods of treatment, e.g., ether in oil, epinephrine, fever therapy and anesthesia.

2. If the onset of an attack is sudden and severe, much time may be lost before the injection can be given.

3. If the attack is well established before treatment is instituted, the response may be delayed or diminished.

With these facts in mind, we felt that if we could keep the bronchial musculature relaxed by a continuous infusion of aminophyllin we could accomplish two purposes. First and most important, the patient could be kept free from the prolonged suffering and apprehension so common in status asthmaticus. Second, the relaxation could be continued over a period of time long enough for the associated edema of the bronchial mucosa to subside and thus hasten recovery. We were also influenced by the startling results frequently obtained by the continuous intravenous administration of penicillin (Priest[5] and others) in subacute bacterial endocarditis.

TECHNIQUE

The technique used is summarized in Table I. We began by calculating twenty-four hour dosage of aminophyllin used in previous treatment. With this as a guide we dissolved the total amount in 2,000 c.c. of 5 per cent glucose in distilled water. This was then given by the continuous intravenous drip method at the rate of 28 drops per minute or 1,000 c.c. per twelve hours. At no time during the procedure did we allow the treatment to be discontinued. If at any time the vein containing the needle showed evidences of inflammation the needle was transferred to another vein, preferably in another extremity. We used the broad volar and dorsal surfaces of the forearms, avoiding the joints as much as possible. This permitted the patient to use the extremity to a limited degree. Number 23 short-bevel needles are recommended. Aminophyllin in the form of the

TABLE II. CONTINUOUS INTRAVENOUS AMINOPHYLLIN THERAPY DOSAGES AND RESULTS OF TREATMENT

Cases	Name	Sex	Age	Duration Asthma (years)	Total Grams Aminophyllin	Number Days	Results
1	H.R.	M.	33	14	19.75	14	Excellent
2	W.M.	M.	48	1.5	29.50	21	Fair
3	B.T.	F.	66	20	11	6	Good
4	R.S.	F.	28	15	13.5	20	Excellent
5	A.S.	F.	66	10	8	7	Excellent
6	M.M.	F.	61	1.5	22	11	Fair
7	A.H.	F.	39	2	12.5	8	Fair
8	M.C.	F.	37	1	12	7	Excellent
9	V.W.	F.	53	14	4	3	Fair
10	J.M.	F.	37	37	14	8	Poor

large 0.5 gm. ampules in 20 c.c. of saline may be used, but the small 2 c.c. ampules ordinarily used for intramuscular injections are satisfactory and more economical. Bed rest is necessary but diet trials can be made.

The dosage of aminophyllin was determined by the measure of relief and control of symptoms. It was necessary in all cases to begin with large doses and then gradually decrease as relief occurred. Careful clinical examinations were made several times a day, and the blood pressure and pulse were frequently recorded. No toxic reactions occurred in this series.

CASE REPORTS

The following case reports are given in order of admission to the hospital (Table II).

Case 1.—H. R. a white man, aged thirty-three years, had attacks of severe bronchial asthma for fourteen years. His asthma was not controlled during a period of three weeks in this hospital. His attacks were of the most severe type, with sudden marked dyspnea, orthopnea, coughing, wheezing, and cyanosis. It was necessary to give him as many as eight or ten separate injections of aminophyllin per twenty-four hours, in dosages of 0.25 to 0.75 gm., depending on the severity of attacks. He was hardly able to eat or sleep and had lost about 10 pounds since admission. He had also received injections of epinephrine, intravenous administration of typhoid vaccine, ether in oil per rectum, and aminophyllin by mouth and per rectum. He had previously received very little relief from bronchoscopic aspiration and from deep ether anesthesia.

Three grams of aminophyllin were dissolved in 2,000 c.c. of 5 per cent glucose in distilled water and given intravenously and continuously at the rate of 28 drops per minute. Response was good. One mild attack occurred during the first twelve hour period. Wheezing practically disappeared on the fourth day and the daily dosage of aminophyllin was therefore reduced from 3 to 2 grams; on the tenth day the dosage was again decreased to 1 gram per twenty-four hours, on the twelfth day to 0.5 gram, on the thirteenth day to 0.25 gram, and then discontinued entirely on the next (fourteenth) day. He received a total of 19.75 grams. The patient's

response was remarkable, and he left the hospital three days later. There was no significant change in blood pressure throughout the fourteen days of continuous therapy, and the pulse decreased from about 150 to about 70. The patient experienced no undue discomfort; a steady decrease in cough and expectoration was noted, with slight drowsiness. The needle was changed five times, but there was no venous thrombosis. Re-examination, six months later, revealed excellent condition, with a gain of about 30 pounds. He has resumed his very arduous occupation, a telegraph linesman, and is able to climb telegraph poles without dyspnea.

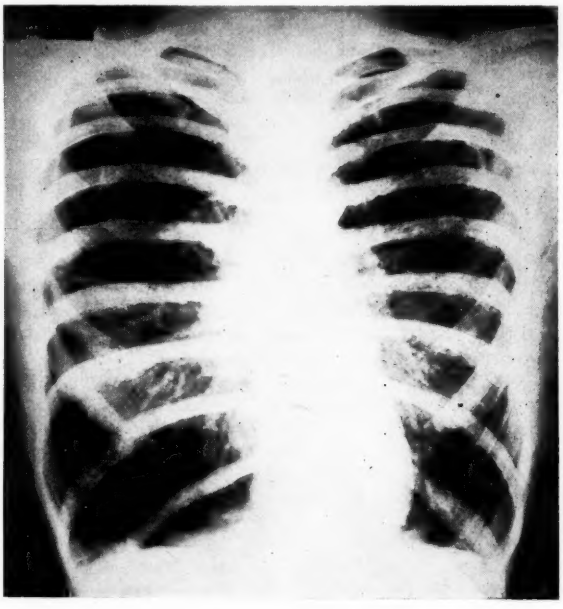

Fig. 1.

Case 2.—W. M., a man, aged forty-eight years, with severe bronchial asthma for about eighteen months, left this hospital three weeks previously and returned with severe asthma. He could hardly eat or sleep. Previous treatment with penicillin, sulfonamides, ephedrin, epinephrine, aminophyllin, typhoid vaccine, and ether in oil had failed. Continuous intravenous aminophyllin therapy was started with an initial daily dose of 2 gm. in 2,000 c.c. of 5 per cent glucose in distilled water. After three days 1.5 gm. were used; on the fifth day the dosage was reduced to 1 gm. but wheezing returned and the dosage was increased again to 1.5 gm., then lowered on the seventh day to 1 gm.; 0.5 gm. was given on the eighth and ninth days. At this point the vein was somewhat inflamed and the asthma was much lessened. Aminophyllin was therefore stopped. The blood pressure showed a slight fall during this nine-day period, but the pulse was not altered. No toxicity occurred. Large nasal polyps were removed at this time, and the patient left the hospital on the sixteenth day. Wheezing had practically disappeared, but asthma returned a few days later. He re-entered the hospital and received another 14.75 grams in a twelve day-period, for a total of 29.50 grams in twenty-one days. He improved again but was not completely free from asthma when he left the hospital.

Case 3.—B.T., a woman, aged sixty-six years, had severe chronic asthma for over twenty years, with numerous previous admissions to this and other hospitals. She had received epinephrine, penicillin, ephedrin, sulfonamides, typhoid vaccine, ether in oil, x-ray treatments, and many injections of aminophyllin. She was admitted in acute distress, with cyanosis, dyspnea, orthopnea, cough and wheezing. She received a total of 11 grams of aminophyllin continuously over a period of six days, with considerable improvement. But a moderately severe thrombosis of the vein occurred on the fourth day, and the patient was very uncooperative; therapy was discontinued much too soon. Her asthma is now mild but still present.

Case 4.—R. S., a woman, aged twenty-eight years, had severe bronchial asthma for fifteen years, with previous admissions to this and other hospitals. She was very apprehensive and had severe asthma. Marked emphysema was present, and she weighed only about 70 pounds. X-ray confirmed the diagnosis of asthma and emphysema and also showed three small areas of spontaneous pneumothorax (Fig. 1). On previous admissions she had received penicillin, epinephrine, typhoid vaccine, and aminophyllin by various routes.

Continuous intravenous aminophyllin therapy was begun with 1 gm. each day for two days, and decreased to 0.75 gm. on the third day; mild wheezing returned and the dosage was increased to 1.5 gm. on the fifth day; symptoms were again well controlled, and dosages were decreased to 1, 0.5, and 0.25 gm. on the seventh, eighth, and ninth days, respectively. Wheezing disappeared and continuous therapy was discontinued in favor of occasional injections of epinephrine and the use of aminophyllin per rectum. Symptoms reappeared in mild degree four days later, and continuous therapy was resumed, beginning with 2 gm. for each of four days, followed by 1.5 gm. on the fifth day, 1 gm. the sixth and seventh days, 0.5 gm. the eighth and ninth days, and 0.25 gm. the tenth and eleventh days. She had a total of 13.5 gm. of aminophyllin during twenty days. The needle was changed several times but no thrombosis occurred. She left the hospital in good condition, with only an occasional mild episode of asthma. She was put on a high-carbohydrate, high-caloric, high-salt diet, plus injections of adrenal cortex extract, and has gained over 30 pounds.

Case 5.—A. S., a woman, aged sixty-six years, with severe bronchial asthma for ten years, was semi-stuporous when first seen. She had previously received epinephrine and two injections of morphine; as a result breathing was almost absent and her condition was serious. She was given 0.25 gm. aminophyllin intravenously and was hospitalized. She received 8 gm. aminophyllin during seven days of continuous therapy, with prompt relief of symptoms. Tachycardia disappeared, the blood pressure was slightly reduced. Wheezing was absent when she left the hospital. Since then she has had mild asthma at times, with symptoms easily controlled by occasional use of aminophyllin, epinephrine, or ephedrin.

Case 6.—M. M., a woman, aged sixty-one years, had very severe asthma for about twenty months, with little relief from previous measures, including intermittent use of aminophyllin, sulfonamides, typhoid vaccine, iodides, apomorphin, and "Gay's" treatment. Continuous intravenous aminophyllin therapy was given for eleven days, with a total of 22 gm. of the drug, but results were only fair. Some wheezing persisted. Bronchoscopic aspiration was then tried but with little relief, and the patient left the hospital with only a little improvement. No toxicity was noted.

Case 7.—A. H., a woman, aged thirty-nine years, with chronic severe asthma for two years. She received 12.5 gm. aminophyllin by the continuous method over a period of eight days. No reactions occurred, and she left the hospital moderately improved. Asthma returned in full force after she returned home.

Case 8.—M. C., a woman, aged thirty-seven years, had asthma for about a year and a particularly severe attack before entrance to the hospital. She was given 12 gm. dissolved in 14 liters of glucose or saline during seven days. Asthma disappeared entirely, and she has been practically asthma-free since she left the hospital.

Case 9.—V. W., a woman, aged fifty-three years, had asthma for fourteen years. She received only 4 gm. of aminophyllin during three days and refused further treatment because she did not like the procedure. She left the hospital three days later, with fair results.

Case 10.—J. M., a woman, aged thirty-seven years, had chronic asthma almost from birth. She received 14 gm. of aminophyllin during eight days, without much relief.

DISCUSSION

Ten patients in status asthmaticus received continuous intravenous aminophyllin therapy. Relief was obtained in almost all cases, with brilliant results in four patients and failure in only one. Relapses occurred in some cases, as was to be expected, as aminophyllin is not a cure-all. Initial dosages varied from 1 to 3 gm. of aminophyllin dissolved in 2,000 c.c. per twenty-four hours, and dosages were decreased as improvement occurred. Dosages were temporarily increased in two of the patients when wheezing recurred, and in each case wheezing quickly disappeared. In these patients we probably reduced amounts too rapidly; a longer, more sustained period with larger amounts of aminophyllin will probably bring more lasting relief. Toxic symptoms were entirely absent. The blood pressure and pulse declined as the asthma disappeared.

Inflammation of the vein occurred in two cases but disappeared in a few days. Similar thrombosis has occurred with continuous intravenous penicillin therapy. We began by using only 5 per cent glucose solution but we now alternate liters of glucose and of physiological salt solution. The salt solution is less irritating but we like to use 5 per cent glucose because it is almost as free from irritation and it is nutritious (50 gm. per liter); glucose is also very helpful to a liver from which glucose may have been driven by frequent administration of epinephrine. We shall continue to use glucose for intermittent injections when we give aminophyllin over a three to four hour period. The incidence of thrombosis of the veins can also be lessened by attention to three small details. The needles should have short bevels; they should be firmly taped in place and the tapes checked at frequent intervals to insure firmness; and the needle should be changed to another vein at the earliest sign of inflammation. The solution must not be allowed to "run dry."

No blood level determinations for aminophyllin were made, as we were unable to find a quantitative method of determination, and to our knowledge one does not exist.

It is important, of course, to use all possible means to find and eliminate the cause of bronchial asthma; hyposensitization continues to be of extreme importance. But when specific measures fail and the usual non-

specific methods are also unsuccessful, we urge others to try continuous intravenous aminophyllin therapy.

CONCLUSIONS

1. Status asthmaticus in ten patients was completely or partially eliminated in nine cases by the continuous intravenous administration of aminophyllin. Relapse may or may not occur when the procedure is discontinued.

2. Dosage consisted of up to 2 or even 3 gm. of aminophyllin dissolved in 2,000 c.c. of 5 per cent glucose in distilled water or of physiological salt solution, alternating; the solution was given at the rate of 28 drops per minute.

3. Large dosages of the drug should be used initially and very gradually reduced as the asthmatic symptoms subside.

4. Aminophyllin can be given in dosages up to 3 gm. per twenty-four hours without undue danger to patients with severe bronchial asthma.

5. Continuous intravenous aminophyllin therapy is strongly recommended for the most severe types of status asthmaticus, the types which have resisted all other kinds of therapy.

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TOXIC THROMBOCYTOPENIC PURPURA FOLLOWING LOCAL SULFATHIAZOLE THERAPY. Donaldson, G. M., and Scarborough, H.: Arch. Dis. Childhood, 20:69, (June) 1945.

The author describes the case of a boy twelve years of age treated with 5 per cent sulfathiazole ointment twice a day because of a mild impetigo. Epistaxis and a generalized purpuric rash started the evening of the second day. On the third day the platelets were reduced to 20,000 per c.mm. and capillary resistance was greatly reduced. There was no history of allergy or of blood dyscrasia in the boy or his family and he had never previously had sulfonamide therapy. Recovery occurred on discontinuance of the sulfathiazole ointment and daily transfusion for five days. After return of the platelet count and capillary resistance to normal levels the application of sulfonamides to the intact skin produced striking reductions in capillary resistance at and away from the site of application. Less striking falls in platelet counts were noted. The author considers that these observations point to the importance of the vascular factor (low capillary resistance) as the basis of toxic thrombocytopenic purpura.

CUTANEOUS REACTION-UNITS

ROGER P. WODEHOUSE, Ph.D.
Pearl River, New York

A REACTION resulting from a cutaneous test is defined as *a wheal surrounded by an erythema.* Both parts of the reaction express its intensity but there is no constant relation between the two. For example, it is found, selecting from a series of fifty-two tests made by the intradermal injection of 0.01 c.c. of pollen extracts of varying concentration, that reactions showing wheals 10 mm. in diameter may be surrounded by erythemas measuring 35 to 60 mm. in diameter. Also from a similar series of reactions, erythemas of 40 mm. in diameter may surround wheals ranging from 6 to 12 mm. in diameter.

It is in recognition of this dual nature of the cutaneous response that the method of visual estimate, expressed by strings of plus signs to indicate "size," has come into general use. The method has in its favor the possibility of giving consideration to both the wheal and erythema in rating the "size" or intensity of a reaction, an advantage which is denied to mensurative methods of recording the reaction at present in use. Unfortunately, however, records made in this way are necessarily subjective and express little more than the emotional and possibly biased response of the observer to his observation.

That there is a quantitative relationship between the excitant and the skin response is to be expected. Indeed such has been shown by several investigators. Harley (1937) showed that in comparative cutaneous tests, if the diameter of the wheal of one were double that of another, it would indicate a potency value of ten or fifteen times in the excitant; or if three times the diameter, it might indicate a potency ratio of twenty times.

Owing to the extreme variability in sensitivity of different sites on the human skin, the most successful use that has been made of the reaction size has been by direct comparison of reactions at comparable sites and far enough apart so that the reactions do not influence each other. Thus Bowman (1934, 1935) was able to distinguish antigenic solutions differing by as little as 25 per cent, providing the compared tests were made 4 inches apart vertically or 1.5 inches horizontally on the upper arm. Pabst, Boatner and Efron (1940) showed that, from a statistical analysis of an adequate number of samples (501), parallel comparative skin tests on the radial and ulnar sides of the forearm showed a significant difference when the exciting substance on the one was twice the strength of that on the other. But when the antigenic strengths were the same in the two positions, there was no significant difference. The observer in such cases has only to decide which, if either, of two reactions is the

From the Lederle Laboratories Division, American Cyanamid Company, New York City. Dr. Wodehouse is an Associate Fellow of the American College of Allergists.

larger. The personal element is here eliminated by keeping the observer in ignorance of the values of the testing materials and not asking him to tell how much larger one reaction is than another.

TABLE I. AVERAGE DIAMETER, IN TWELVE TESTS, OF WHEALS (W) AND ERYTHEMA (E) AND THEIR CORRESPONDING REACTION VALUE (E–W)W

Serum Dilution	w	e	(e–w)w
1:10	12.58	47.08	434
1:20	11.83	48.33	432
1:40	11.58	45.83	397
1:80	11.08	43.33	357

Though these three examples, selected from a considerable number recorded in the literature, serve adequately to show that there exists a relation between the strength of the antigen and the intensity of the reaction, I find no report that indicates numerically what this relation may be, closer than that of Harley.

In order to evaluate the cutaneous response in terms of antigenic strength, it is necessary to have a means of measuring the former, comparable in accuracy with the simple method of determining relative strengths of antigen by dilution. For simplicity the cutaneous response may be regarded as the product of two variables, the wheal and erythema. In this sense it is two-dimensional, but these dimensions are curiously related. If the erythema is increased while the wheal remains constant, the reaction value will be increased in proportion indefinitely. If the wheal is increased while the erythema remains constant, however, the reaction value is increased only up to the point where the wheal begins to encroach on the erythema. The wheal's further increase causes the reaction value to diminish, reaching zero when the wheal coincides with or obliterates the erythema, for a wheal without erythema is not a reaction. For example, it is found that intradermal injections of 0.01 c.c. sterile saline regularly give wheals 4 to 7 mm. in diameter, and those of 0.05 c.c. give wheals of 10 mm. or more in diameter, but these are without erythemas so their reaction values are zero.

If the wheal and erythema are regarded as of equal value, the point of encroachment upon the erythema by the wheal is where the diameter of the latter becomes greater than one-half of the over-all diameter of the former, in other words, greater than the excess of the erythema over the wheal.

Accordingly, I have chosen the unit of cutaneous reaction as a wheal 1 mm. in diameter, surrounded by an erythema with a diameter of the same amount in excess, that is to say of 2 mm. in over-all diameter. Any increase in the erythema, or of the wheal together with the erythema, providing the former does not encroach on the latter, denotes a proportionate increase in the intensity of the reaction.

Making use of this unit, cutaneous reactions may be simply expressed by multiplying the wheal diameter by the excess of the erythema diameter over that of the wheal in millimeters. Thus $(e\text{-}w)\ w = n$

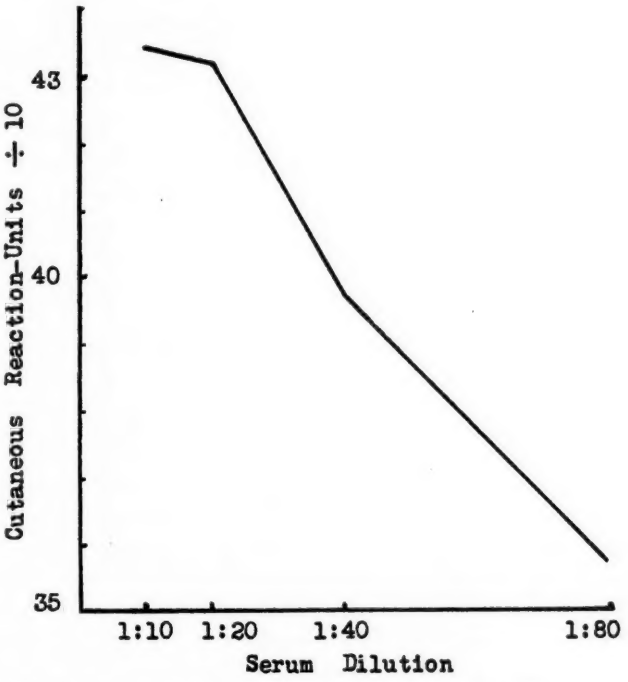

Fig. 1. Serum L. G. Dilution Curve. Reactions of sensitized sites to 0.01 c.c. mountain cedar, 100 units per c.c. Average of twelve recipients.

In this equation e equals the over-all diameter of the erythema, w equals the diameter of the wheal and n equals the number of cutaneous reaction-units. Expressed in this way, the unit reaction becomes $(2-1)1=1$. A reaction with twice the wheal and twice the erythema becomes $(4-2)2=4$, or with ten times the wheal diameter and ten times the erythema diameter, it becomes $(20-10)10=100$.

The increase by squares in the value of n, of course, accrues from the two-dimensional character of the response. If the reaction is regarded as one-dimensional, as it could as well be, the unit-reaction would be expressed as $\sqrt{(2-1)1=1}$, and a reaction with the wheal and erythema both twice as large would become $\sqrt{(4-2)2=2}$ or, with both parts increased ten times, would be $\sqrt{(20-10)10=10}$. It seems that this treatment would unnecessarily complicate the calculations, so for the present studies I have chosen to regard the reaction as two dimensional.

TABLE II. REACTIONS OF SITES SENSITIZED TO J.B. SERUM OF VARIOUS DILUTIONS

Dilution	1:50		1:100		1:200		1:400	
Recipient	w	e	w	e	w	e	w	e
VK	10	50	9	50	10	60	9	40
MC	12	50	8	45	9	40	9	30
AB	10	40	11	55	9	40	8	50
Average	10.7	47	9.3	50	9.3	47	8.7	40
Reaction Units	388		378		351		272	
Dilution	1:125		1:250		1:500		1:1000	
FM	9	15	9	15	6	0	7	0
FF	10	40	10	55	8	30	7	25
BM	10	60	8	40	7	45	6	0
Average	9.7	38	9	37	7	25	6.7	8.3
Reaction Units	274		252		126		107	

It should be borne in mind that the use of two dimensions in establishing this unit is purely a mathematical concept and does not attempt to present a complete picture of the cutaneous reaction. The wheal alone is three dimensional; Abramson and Gorin (1939) have pointed out that its thickness during development varies to some extent independently of its length or breadth. Moreover, Lewis (1927) has shown that the reaction as a whole is a triple response, consisting of a red reaction, a wheal and erythema. We are not concerned with the red reaction because it is quickly obliterated by the wheal, but before this has happened there appears an erythema or flare, as called by Lewis, which is replaced or extended by a flare which later results from the development of the wheal. However, for practical purposes, it appears that the average diameter of the wheal and of the final erythema may suffice.

APPLICATIONS

Those who have studied the phenomena of local passive transfer have found that the serum from a sensitive individual used to sensitize the skin of a normal recipient may be diluted several to many times and still produce reactive sites. Moreover, as would be expected, the size of the reactions obtainable from these sites declines as the concentration of the serum is reduced. This was first observed by Levine and Coca (1926) who recorded the sizes of their reactions by means of ink tracings of the wheals and erythemas. These showed that both declined continuously with the decreasing serum concentration.

Their experiments have here been imitated, substituting measurements in terms of the unit just described for their ink tracings. The serum of a patient sensitive to the pollen of mountain cedar was used in dilutions of 1:10, 1:20, 1:40 and 1:80. Sites were sensitized on each of twelve recipients with the four dilutions by the intradermal injection of 0.05

c.c. of each. Four sites were chosen as uniformly placed as possible in each recipient. There were two on each upper arm, four or more inches vertically apart and symmetrically placed on opposite arms. Dilution

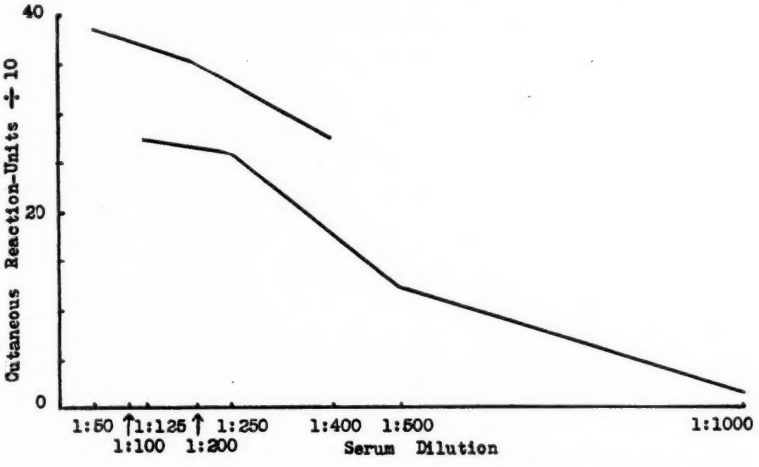

Fig. 2. Serum J. B. Dilution Curves. Reactions of sensitized sites to 0.01 c.c. timothy, 100 units per c.c. Averages of three recipients each.

1:10 was always placed opposite 1:40—in five of the recipients in the upper positions and in seven on the lower. Dilution 1:20 was always placed opposite 1:80—in five of the recipients in the lower positions and in seven in the upper.*

This was done to equalize any consistent differences that there might be between the upper and lower positions. Three days later all sites were tested with 0.01 c.c. of 100-unit mountain cedar pollen extract. The average diameters of the wheals and erythemas are shown in Table I (columns 2 and 3).

Both parts of the reaction are found to decline, on the average, with the diminishing concentration of the serum, except the erythema from the 1:20 dilution which rises slightly. However, when the reactions are expressed in terms of cutaneous reaction-units, all decline with the serum-concentration. These relations become quite clear when the values of the cutaneous reactions and antigenic concentrations are plotted co-ordinately (Fig. 1). The tendency of the curve to flatten at the top shows that any further increase in the serum concentration would probably not produce a much larger reaction with the antigenic concentration used. On the other hand, if the curve is projected in the opposite direction, it is roughly estimated to reach the level of zero-reaction at about two more steps in the dilution series or at a dilution of 1:320.

*The experiment was planned to include fourteen recipients with seven sensitized in each pattern, but some of the sensitized sites were lost on two recipients.

The serum of another patient, sensitive to timothy, was examined for reagin content. From a preliminary short series dilution test it had been estimated that the reaginic activity of this serum would vanish at a dilution of about 1:1,000. Two sets of dilutions were made, 1:50, 1:100, 1:200, 1:400 and 1:125, 1:250, 1:500, 1:1,000. Three recipients were used for each set. Sites were chosen on the upper shoulder and scapula. These were sensitized in the first group of three with dilution 1:50 opposite 1:200 and 1:100 opposite 1:400, in the second group with 1:125 opposite 1:500 and 1:250 opposite 1:1,000. No further attempt was made towards adjustment of positions since these appear to yield no consistent irregularities in value. Three days later, all sites were tested with 0.01 c.c. of timothy, 100 units per c.c. (Table II). Although there is considerable irregularity in the sizes of the wheals and erythemas, when these are averaged for the three recipients in each group and their reaction values plotted (Fig. 2), they assume a rather orderly arrangement. The two curves are approximately parallel so that they are mutually confirmatory. The fact that they are at different levels indicates that the average susceptibility of one group of recipients was higher than that of the other, the result of the well-known individual variation in human skin sensitivity.

Besides the examples in serum dilution given above, the cutaneous reaction-unit has been found a convenient means of measuring and graphically recording the effect of antigen dilution on the intensity of the reaction, the reverse effect of antigen dilution on the retest reactions in both *in vitro* and *in vivo* neutralization tests, and on the effect of the time intervals between sensitization and testing. It offers a simple numerical system of recording reaction intensities.

SUMMARY

Cutaneous reaction-units may be expressed as $(e - w)w = n$ if n equals their number and e and w the diameters of the erythema and wheal, respectively, of a cutaneous reaction.

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TREATMENT OF INSULIN ALLERGY
With Report of a Case

SAMUEL S. BURDEN, M.D., F.A.C.A.
Jenkintown, Pennsylvania

SINCE the discovery of insulin and its use in the treatment of diabetes mellitus, numerous reports of allergic reactions to the commercial product have been reported. Only a small percentage of these cases were proven to be definitely due to crystallin insulin.[10,22] In reviewing the literature written on the subject, it becomes obvious that most reports have been concerned mainly with presenting evidence of the existence of insulin allergy. The methods of treatment of these cases have been quite varied and in the majority of the cases, unsuccessful. Too few have been concerned with the underlying immunologic principles. The reason is quite evident when we realize that the incidence of insulin allergy is rather small. The reported incidence of allergic response to insulin varies from .04 to 30 per cent. Collens, Lerner and Fialka[5] reported that out of 407 cases of insulin treated diabetics, 7.3 per cent showed protein reactions. Hallerman[8], in a total of 541 diabetics treated with insulin, found only two cases with allergic symptoms severe enough to warrant discontinuance of insulin therapy and he concluded, therefore, that insulin allergy was so rare as to cause little concern. Allen and Scherer[1], in their review, conclude that of all cases sensitive to insulin only 1 to 2 per cent will show systemic reactions manifested by urticaria, edema, pallor, flushing, fall in blood pressure, circulatory collapse, and gastro-intestinal symptoms. The other 98-99 per cent manifested mild to severe local reactions at the site of the injection. Yasuna[22], in his review concludes that "since the severity of the disease in persons developing diabetes in the fifth to seventh decades often is mild, and since the great preponderance of cases showing generalized allergy to insulin were in the older age groups, the problem of insulin therapy is not as acute as in the young age group. Therefore, it is possible to discontinue insulin in many patients showing generalized sensitivity to the medication."

The above figures and conclusions clearly indicate the reason for the tendency to treat the problem of insulin allergy as little more than a curiosity and to treat the individual case by withdrawing the medication. That is all very well in the patient who can be controlled on diet alone. But what of the occasional young or old diabetic who must have insulin? That person, I am sure, will not be satisfied with statistics and will demand that something be done for him. Bayer's case[2], following the administration of 5 units of insulin developed severe abdominal cramps, generalized eruption and a "sense of choking." Herold[11] reports the

Dr. Burden was formerly Captain, MC, AUS, and Chief of Allergy Clinic, Walter Reed General Hospital, Army Medical Center, Washington 12, D. C.
Studies and treatment prior to March 17, 1946, at Walter Reed General Hospital were carried out by Dr. L. L. Pennock, formerly Major, MC, AUS.

case of a twenty-three year-old diabetic who after 20 units of insulin developed severe urticaria, angioneurotic edema and "asthmatic wheezing and choking sensation," necessitating the repeated administration of epinephrine. Allen and Scherer's[1] case was that of a forty-eight year-old woman who after the administration of insulin developed urticaria and angioneurotic edema of the face, mouth and throat to such a degree that breathing became difficult and she was in great distress. These authors also mention in their report several reported cases in which failure of insulin to exert its usual effect was attributed to allergy and indicated the danger that might result from this phenomenon. I have cited the above cases to emphasize the fact that insulin allergy may have serious import. Some of those cases had to have insulin and some method had to be devised whereby their sensitivity could be decreased.

METHODS OF TREATMENT

In order to treat properly a case of allergy to commercial insulin, it must first be determined whether the allergy is to insulin itself or to some other protein in the commercial preparation. Thus testing with pure crystalline insulin will eliminate the possibility of the allergic reaction being due to the pancreatic tissue of the animal. Hughes[12] reported a case of urticaria following protamine zinc insulin and, after study, concluded that the sensitivity was to the protamine. Tuft[17] in his "Review of Insulin Hypersensitiveness" reported two cases; one due to allergy to an extraneous protein in the commercial preparation, and one that showed skin reactions both to crystalline insulin and to the commercial product. Where the allergy is proven to be due to other than the insulin factor, a change of product or the use of crystalline insulin will solve the problem. However, when the insulin factor is involved, then only one of two methods of treatment can be followed: either control of the diabetes by strict diet alone or an attempt at desensitization or hyposensitization. Various methods have been used in attempting to produce desensitization or hyposensitization; and histamine as well as insulin has been employed as the antigen.

Bayer[2] employed the rapid method of desensitization in his case starting at 9:15 a.m. and continuing until 5:20 p.m. During this time, seventeen intradermal injections ranging from .001 unit to 1 unit were given. An eighteenth injection consisting of 5 units was given hypodermically at 5:20 p.m. This patient was able to tolerate 10 to 15 units of insulin daily following this treatment, but within two weeks time urticarial reactions reappeared.

Corcoran's[6] patient could not be controlled on diet alone, and he treated his patient by the rapid method of desensitization beginning at 7:30 a.m. and continuing until 9:00 p.m. During this time a total of thirty injections were given at intervals varying from five minutes to forty minutes. Various routes of administration were used during the course of treat-

ment including intradermal, subcutaneous and intravenous. The highest intradermal dose was 4 units; the highest subcutaneous dose 40 units; and the highest intravenous dose 30 units. At the end of twenty-four hours the reactions to intracutaneous tests were entirely negative and following this the patient was able to tolerate 20 units of insulin daily.

Allen and Scherer[1] also used the rapid method on their patient following an operation for an empyema of the gall bladder. This patient postoperatively developed acidosis with a CO_2 of 21.1 vol. per cent and a blood sugar of 295, and was in a critical condition. Treatment was begun with ¼ unit of crystalline insulin. The injection was repeated at one-half hour intervals, increasing the dosage 50 per cent each time, unless the local reaction was too severe. At the end of six hours the patient was receiving 3 units. This dose was repeated hourly during the night. The following morning her CO_2 was 64.5 vol. per cent. The patient's clinical condition improved and the dosage of the insulin was increased. Eventually, the patient was able to tolerate 40 to 50 units of crystalline insulin. Subsequently the patient was treated in a similar manner with commercial insulin. Improvement continued so, after two weeks, treatment was discontinued. Eleven days after treatment was discontinued skin tests were performed. There was an immediate local and generalized reaction manifested by local swelling, pruritis, and some swelling of the lips. Thus there had been a return of extreme hypersensitiveness.

Slower methods of desensitization with insulin have been attempted. Herold[11] treated his patient by giving daily injections beginning with 1/250 unit and gradually increasing every day. After two months the patient was able to tolerate 24 units of insulin daily without any allergic reaction.

Bryce[4] reported a case which she desensitized, first, by daily and then by twice daily injections, beginning with minute amounts and increasing until the patient was able to take the needed amount twice a day.

Davidson[7] reported the case of a sixty-two year-old diabetic who developed severe urticaria following insulin injection. In addition to urticaria, it was also found that her diabetes was difficult to control even with increased dosage of insulin and rigid diet. Desensitization was carried out beginning with 1 unit and increasing by 1 unit every three or four days up to 8 units. Her blood sugar almost reached normal and her urine became sugar-free. The author, however, is not certain whether the desensitization procedure had any effect on the outcome of the case, since her reactions had almost completely disappeared before desensitization was instituted.

Methods other than the rapid and slow desensitization with insulin have been used. Thus, Kaufmann[14] described three cases of severe reaction to insulin which were relieved by one or two intracutaneous injections of from 4 to 6 units. Hughes[12] employed "Hapamine;" four

weeks after treatment was instituted there still had been no return of urticaria. Collens, Lerner and Fialka[5], failing to desensitize their patients by the slow method with insulin, employed histamine phosphate beginning with .1 mg. and gradually increasing until the patient was receiving 1.0 mg. per dose. Injections were given three times weekly for thirteen doses. Following the last injection of histamine the patient was able to tolerate 10 units of insulin daily; six months later he was taking 15 units of insulin daily without any reactions. Karr, Kreidler, Scull and Petty[13] sensitized a rabbit with gradually increasing doses of their patient's serum. This rabbit serum showed allergic antibodies when using insulin as the antigen. Some of this rabbit serum was then given to the patient. The patient demonstrated a fall in her insulin requirement and after about a month it was possible to discontinue insulin entirely. This last case tends to fit into the concept of hyposensitization by producing an abundance of free circulating antibodies which combine with the antigen and thus protect the living cells.[21] Urbach[19], in discussing the treatment of insulin allergy, mentions, in addition to the slow and rapid methods of desensitization, the method of skeptophylactic de-allergization. In this procedure he recommends the administration of ½ to 1 unit of insulin subcutaneously forty-five minutes before the main injection. Urbach defines de-allergization as a process whereby antibodies are neutralized, and has demonstrated loss of sensitivity in the lung and uterus of experimental animals when employing this method, using food digests (propeptans).[20] The principle of this treatment is based on the demonstration by Besredka[3] that the pre-administration of a given antigen affords complete protection against what would otherwise be a fatal dose of allergen. According to Urbach, de-allergization differs from hyposensitization in that the latter is a method whereby clinical insensitivity is due to the production of an excess of free circulating antibodies by the repeated administration of small doses of antigen. In his treatment of food allergy Urbach employs food digests (propetans) rather than the native protein maintaining that the degree of hypersensitiveness may be so high that even very small quantities of the particular food may produce anaphylactic symptoms. The food digest, on the other hand, will produce a state of anti-anaphylaxis by bringing on a microshock sufficient to neutralize temporarily the available supply of antibodies. The phenomenon of de-allergization is produced by following the administration of the specific propeptan by the native food protein. The neutralization of the antibodies that follows results in clinical insensitiveness.

In the case to be reported, due to the failure of other methods of desensitization, as will be described, treatment was carried out according to Urbach's method with some modifications. Hughes[12] recently reported a case of sensitivity to protamine insulin in which skeptophylactic de-allergization failed to occur. It was thought advisable, therefore, to try Urbach's method, with two modifications. Rather than use an arbitrary

dose of ½ to 1 unit of insulin, as the pre-administration dose, the dose was determined on the basis of the size of the wheal produced on intradermal testing. This course was suggested by Hansel's[9] method of co-seasonal treatment of hay fever. It was thought that if neutralization of antibodies was to be accomplished, ½ to 1 unit might be too great a dose for a micro-shock, since cases have been reported in which the initial dose of insulin for the desensitization had to be .0001 unit or less, in order to administer an amount which could be tolerated.[10] The dose of insulin selected, therefore, was the amount which produced a wheal approximately 15 mm. in diameter and in this particular case it was 1/200 unit. The second modification was to administer the small dose intradermally rather than subcutaneously. This also was suggested by Hansel's[9] method of co-seasonal treatment of hay fever, since a great similarity was believed to exist between the daily administration of insulin and the daily inhalation of pollen. It was also thought that if neutralization of antibodies did not occur, and if relief of symptoms would actually be due to an increase of circulating antibodies, the intradermal route was the best way to produce an excess of antibodies quickly.[18]

REPORT OF CASE

The patient, aged twenty-five years, was admitted to Walter Reed General Hospital on November 25, 1945, with a diagnosis of diabetes mellitus. The patient had been an airplane mehanic for three years before induction into the army in April, 1944. There was no familial history of diabetes and no personal or familial history of allergic disease. On July 2, 1945, he was hospitalized at a general hospital on Tinian Island because of severe abdominal pain and vomiting of twenty-four hours duration. He stated that he previously had been in apparently good health, but after careful questioning he admitted that, for about three months prior to his admission to the hospital, he had noted frequency of urination as well as polyuria, polydypsia and polyphagia, and a loss of about 40 pounds in weight. On routine examination of his urine a positive qualitative test for sugar was found and a subsequent fasting blood sugar was found to be above normal limits. Treatment was started with protamine zinc insulin, and about three weeks after treatment was instituted, he first noted that at the site of each injection he would develop a large indurative red reaction which persisted for twelve to fourteen hours and necessitated the application of hot compresses. Subsequently, he noted local urticaria in addition to the local reaction, and still later generalized urticarial reactions developed. Skin tests were performed overseas with insulin, and a positive reaction was found. It was recommended that he receive "desensitization treatments" after he was returned to the United States.

For three months after his return to the United States he was hospitalized at a general hospital and continued to receive insulin daily. Generalized urticaria developed after each injection. On arrival at Walter Reed General Hospital skin tests were performed using various insulin products. He had a marked reaction to regular insulin, "a less marked" reaction to one brand of protamine zinc insulin and globin insulin, and a slight reaction to another brand of protamine zinc insulin. Skin tests with beef and pork were negative. Rapid desensitization with protamine insulin was attempted by the intradermal route beginning with 1/1000 unit and increasing the dose at ten to twenty-minute intervals until 1 unit was reached. A total of ten injections were given. Urticaria following daily administration of

Fig. 1. Intradermal skin tests with varying doses of regular insulin. Each dose was contained in 0.05 c.c.

Fig. 2. Intradermal skin tests with varying doses of regular and crystalline insulin. R—regular insulin. C—crystalline insulin. Each dose was contained in 0.05 c.c.

25 units of globin insulin persisted. Subsequently desensitization with histamine was attempted but this also failed to alleviate the symptoms. The patient was placed on benadryl, 50 milligrams three times daily, and this gave him complete relief of his urticaria for three weeks, after which the urticaria returned and persisted in spite of the continued administration of benadryl.

On March 17, 1946, the patient was referred to allergy clinic for further study and recommendations. Skin tests with regular insulin were performed, and they revealed positive reactions beginning with 1/200 unit (Fig. 1). Passive transfer tests failed to reveal the presence of skin-sensitizing antibodies (reagins). The patient's ward officer was instructed not to give the patient any more insulin, and control of the diabetes was attempted on a strict dietary regime. In the meantime hyposensitization therapy was instituted on a bi-weekly schedule by the intradermal route. The first dose consisted of 1/1000 unit, the second, 2/1000 unit, repeated on three subsequent occasions, after which he received one dose of 1/200 unit. In all, he received six intradermal injections between March 25 and April 5, 1946. At that time his blood sugar was over 200 mg. per cent, he had lost weight, and therefore his ward officer insisted on resuming daily doses of insulin. Since hardly enough time had elapsed for desensitization or hyposensitization to have taken place, the possibility was considered of treating this patient by the skeptophylactic de-allergization method with the modifications described above. The ward nurse was instructed to give the patient 1/200 unit of regular insulin, intradermally, three-fourths to one hour before administering 20 units of globin

insulin. This form of therapy was instituted on April 6, 1946. On that day he had two to three urticarial lesions for the first time since the insulin had been discontinued. After that he had no more urticarial lesions although he continued to receive 20 units of globin insulin daily, preceded by the 1/200 unit of regular insulin intradermally. He noted also a decrease in the size of the local reaction.

This form of therapy was continued until April 25 when the patient went on a three-day pass. He continued to take 20 units of globin insulin daily, but discontinued the intradermal dose. When he returned to the hospital he continued to take his daily insulin, increasing the dose to 25 units, but the intradermal dose of 1/200 unit was still omitted. The patient remained free of urticaria, although he did remark that there was an increase of erythema and induration at the site of the injection.

On May 1 skin tests were repeated using crystalline insulin in addition to regular insulin. The reactions to the regular insulin were essentially the same as they were on March 18. The reactions to crystalline insulin, although not as marked as to the regular insulin, were definitely positive beginning with 1/20 unit and markedly positive to ½ unit (Fig. 2).

On May 9 the patient began complaining of the appearance of one or two red blotches appearing in the late afternoon or evening and itching only very slightly. On May 13 there was a complete recurrence of the generalized urticaria. He was again placed on the program of receiving 1/200 unit of insulin intradermally three-fourths to one hour before his usual dose of insulin. Again he had a complete cessation of the generalized urticarial reactions. On May 17 the patient reported that he was receiving 25 units of globin insulin daily, and that so long as he received his intradermal dose at least three-fourths of an hour before his regular dose he would have no urticaria. However, on two occasions he had received his intradermal dose only ten minutes before his regular dose and, on both occasions, generalized urticaria resulted. Since his skin reaction to the 1/200 unit had decreased in size, the dose was increased to 1/100 unit, and the time interval was more carefully observed.

On May 21, 1946 the patient was ready to leave the hospital, having no urticarial reactions at all and such slight local reactions that he was conscious of no discomfort. He was instructed in giving himself the intradermal injections and requested to communicate with the clinic on his progress.

Just before the patient left, a blood specimen was drawn for the purpose of performing additional passive transfer tests. The same recipient was used as was on the first occasion and this time there was a questionable reaction to ½ unit of both regular and crystalline insulin. When another recipient was used there was a definite reaction to regular insulin and a slight reaction to crystalline insulin.

On June 17, 1946, a letter was received from the patient stating that he was well but beginning to develop a few "hives" during the evening. He stated that these urticarial lesions were not severe enough to cause him any discomfort. The patient was instructed to increase his morning intradermal dose of insulin to 1/50 unit and, if that failed to prevent the urticaria occurring in the evening, to revert back to the 1/100 unit intradermally in the morning followed by a second 1/100 unit intradermally in the early afternoon. The morning intradermal dose, of course, was to be followed by his regular dose of globin insulin whereas the afternoon intradermal dose was given alone.

On June 29, a second letter was received from the patient stating that he had increased the intradermal dose as directed and that, although he had continued this for ten days, he was still having a few "hives" in the evening. He further stated that he was beginning to "spill a little sugar in the evening." The patient said that he would now try the second suggestion and report further.

On July 17, patient again wrote that since his last letter he had been taking 1/100 unit of insulin intradermally, morning and afternoon, and that institution of this procedure had resulted in a complete cessation of the evening urticaria.

The above train of events is quite interesting since it so closely resembles the course often taken in the co-seasonal treatment of hay fever. The exposure to a prolonged action insulin product is also comparable to twenty-four hour exposure to atmospheric pollen.

DISCUSSION

This case has been presented primarily because it represents a slight departure from the usual methods of treatment of insulin allergy and with apparently good results. If this method proves to be equally successful in other cases, it would then offer a means of giving quick relief from very unpleasant reactions without the discontinuance of insulin administration. As to throwing more light on the immunologic principles involved, I am afraid that I have contributed nothing. The patient was definitely allergic to the insulin factor as proved by a positive reaction to crystalline insulin. Although no skin sensitizing antibodies (reagins) were demonstrated on the first passive transfer, they were demonstrated on the second attempt. It is interesting to note that there was a greater reaction on one recipient than on the other. The recipient, who showed the doubtful reaction on the second transfer, showed no reaction on the first and it is possible that we were dealing here with an individual whose skin was not receptive.[16] Because of this likelihood, it becomes impossible to attribute the appearance of a marked passive transfer reaction on a new recipient to an increase in circulating antibodies produced by the treatment. That a state of hyposensitization or refractoriness was produced, however, cannot be denied as evidenced by the relief of symptoms both at the beginning of treatment and at the resumption of treatment following the relapse when the intradermal doses had been discontinued. The mechanism involved in this state of refractoriness, however, is not clear. If skeptophylactic de-allergization occurred, then there was a neutralization of fixed antibodies but obviously not a permanent one. This fact however can neither be proven nor disproven. Vaughan,[21] in discussing the co-seasonal treatment of hay fever by small dose therapy, stated very definitely that the process was not one of antibody exhaustion, since skin tests and passive transfer tests indicated a persistence of reagins in the blood. However, in support of the possibility that the refractoriness may be due to saturation of tissue antibodies is the statement by Zinsser[23] that the fact that reactive antibodies appear free in the circulating blood does not preclude the possibility that fixed tissue antibodies have been neutralized. He further states that the neutralization of the fixed antibodies may actually result in a reaction whereby the living cell produces more antibodies and thus results in a superabundance of free antibodies or reagins in the blood. Ratner[15] states that the refractoriness of anti-anaphylaxis or desensitization may result

either from a partial or complete saturation of tissue antibodies with antigen or by the saturation of the blood with a large amount of circulating antibodies. According to Zinsser, however, both these reactions may occur simultaneously as part of the same mechanism. The relief offered by Karr et al[13] to their patient by the administration of sensitized rabbit serum appears definitely to have been due to the introduction of a large amount of circulating antibodies which prevented the antigen from reaching the fixed tissue antibodies.

To attempt to explain further the mechanism involved in the relief given this patient would purely be more conjecture with an admixture of a brand of "rocking chair philosophy." Harten and Walzer[10] aptly state that, in view of the fact that the mechanisms involved in the production of allergic reactions may differ in the various forms of insulin sensitivity, it would be foolhardy to attempt an explanation of the effect produced by specific treatment. Thus Tuft[17] in 1928 demonstrated that in addition to skin sensitizing antibodies (reagins), there were also present in some people allergic to insulin a precipitin antibody to insulin. Tuft also showed that in his case, reagin persisted after the precipitin antibodies had disappeared. In some cases, insulin allergy, like other types of acquired allergy, has been very transitory. All these facts merely indicate that further and more thorough immunologic studies must be carried out in the field of insulin allergy before the question of specific treatment can be intelligently undertaken.

SUMMARY

1. Although systemic allergic reactions to insulin are comparatively rare, they may occur with intensity severe enough to necessitate some form of specific treatment, particularly in those cases that cannot be controlled on a strict diet.

2. Various forms of treatment are reviewed, including slow and rapid desensitization with insulin, desensitization with histamine and hapamine, transference of specific antibodies from insulin-sensitized rabbit serum, and skeptophylactic de-allergization as described by Urbach.

3. A case of insulin allergy is reported which was completely relieved by a modification of Urbach's method of skeptophylactic de-allergization. The patient was given 1/200 unit of insulin intradermally three-fourths to one hour before the required dose of insulin. The intradermal dose was determined on the basis of the dose sufficient to produce a wheal approximately 15 mm. in diameter. This modification was suggested by Hansel's method of co-seasonal treatment of hay fever.

4. The mechanism of specific desensitization to insulin hypersensitiveness is not clear, and further immunologic investigations are necessary before this phenomenon can be better explained.

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PURPURA INDUCED BY THE INITIAL INJECTION OF A PERTUSSIS VACCINE. P. Freud, and W. B. Greenberg. Arch. Pediat., 63: 157-165, 1946.

The authors review the literature of reactions following the injection of pertussis vaccine and observe that purpura is rare and has in the past occurred only after repeated injections. They report the first case in which the initial injection of pertussis vaccine was followed by a generalized purpura.

The patient was a one-year-old negro male infant who was injected with 1 c.c. of the New York City Health Bureau pertussis vaccine (Mishulow). Twenty-four hours later a bright red petechial rash was noted involving the dorsum of the hands, the extremities and buttocks. The child was thought to have had fever preceding the appearance of the eruption. The child's personal and family histories were negative for allergy and his past history was otherwise non-contributory. An erythematous indurated area about the size of a penny was noted over the lateral aspect of the left deltoid muscle, the site of the injection. The right forearm, where no injection was given, was edematous with numerous petechiae. The Vollmer patch and Wassermann tests were negative. Blood studies were made, the most striking finding being a gradual reduction in platelets.

The child ran an uneventful course and was discharged after ten days. Five months later he was given 0.10 c.c. of the same pertussis vaccine intradermally,

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EVALUATION OF INTRAMUSCULAR INJECTIONS OF SPECIFIC EXTRACTS IN THE TREATMENT OF ACUTE POISON IVY DERMATITIS

J. B. HOWELL, M.D.
Dallas, Texas

SHOULD poison ivy extracts be used for the treatment of the acute dermatitis? In view of the high incidence of dermatitis from this plant, the answer to this question is of practical as well as of theoretical importance. It appears that it was Schamberg[7] who first popularized the oral use of an extract of *rhus toxicodendron* for the treatment of poison ivy dermatitis. He reported that tincture of *rhus toxicodendron* had a favorable influence in attacks of ivy poisoning in preventing an extension of the process and in abbreviating the duration of the attack. He maintained that no necessity for injections existed, because oral therapy was sufficiently satisfactory. Strickler[12], commenting on the rationale of non-specific topical therapy in rhus dermatitis, said that the weakness of this mode of treatment is the attempt to overcome a specific inflammatory reaction with non-specific remedies. It occurred to him that the employment of the active principles derived from the plants, which had produced the dermatitis, represented the rational therapeutic method of procedure. Strickler reported that as a rule, to which there are few exceptions, within twenty-four hours after the first injection of an alcoholic solution of poison ivy extract, the itching associated with rhus dermatitis disappeared completely or was greatly modified. The skin was usually restored to normal in four to five days after treatment was instituted except in those generalized cases of dermatitis venenata in which the restoration of the skin to normal may be more delayed.

The Council on Pharmacy and Chemistry admitted rhus preparations to New and Non-Official Remedies in 1926.[11] This recognition was based chiefly on the favorable reports of Schamberg[6,8], Strickler[13,14], Alderson,[1,2] Bivings,[3] and Williams and MacGregor[15,16] that patients with rhus dermatitis were remarkably benefited by the administration of the extracts. It is important to remember that there were no control cases considered by these authors. The introduction of this measure was timely as it occurred in 1916-24, during the period when medical minds were constantly searching for a specific serum for infectious diseases and other disorders for which there were no specific chemotherapeutic remedies.

It was believed necessary to administer the specific extract of poison sumac, poison oak, or poison ivy depending on which plant allergen the patient contacted. Our present-day concept is that the same dermatitis-producing fraction is common to all three plants.

From the Department of Dermatology and Syphilology, Southwestern College of Medicine, Dallas, Texas.
Read by Dr. Rudolf Baer at the meeting of the American College of Allergists, San Francisco, California, June 28 to 30, 1946.

Since the favorable reports of Schamberg, Strickler, and others, the opinions concerning the therapeutic value of poison ivy extracts have been widely divergent. Thus for example Williams and MacGregor[15,16] considered that the method was an effective form of therapy while Pusey[5] and Morrow[4] denied that it had any beneficial effect. In order to shed further light on this problem Dr. Shelmire and I undertook the following series of controlled investigation.

A COMPARISON OF THE EFFECT OF INJECTIONS OF SPECIFIC AND NON-SPECIFIC SUBSTANCES ON THE COURSE OF IVY DERMATITIS

Forty patients with acute poison ivy dermatitis were studied. Their eruptions occurred during the spring and summer months and were seen in the private practice of Dr. Bedford Shelmire and myself. Twenty-three patients were given from one to four intramuscular injections of poison ivy extract (Lederle) during the course of their eruption. Seventeen patients were used as controls and were given from one to four injections of either crude liver extract or proteolac (Searle) intramuscularly or of strontium bromide intravenously. All patients were allowed to use starch bathing, wet dressings, an anti-pruritic shake lotion or emulsion for the symptomatic treatment of itching and burning. In each case efforts were made to discover accurately the number of days required for the "cure." The estimates were based chiefly on the period which elapsed before the disappearance of the rash and the subjective symptoms. The followup of the cases was difficult and necessitated keeping contact with the patient by phone, by correspondence and through frequent visits to the office for observation.

The patients who received the specific extract by injection were not able to sleep any better, did not have fewer cycles of pruritus, less discomfort or any appreciable benefit from injections given before or during the height of the reaction.

In both groups, an occasional patient stated that itching stopped for a few hours soon after receiving the injection. There was absolutely nothing that could be considered specific or strikingly beneficial from the use of poison ivy extract. In this connection it should be mentioned that Sharlit[9] and others have observed that injections of absolute alcohol subcutaneously in poison ivy dermatitis and in similar pruritic eruptions are often followed by a lessening of the subjective symptoms. Perhaps the improvement in Strickler's patients was due to the alcohol instead of the specific allergen of the rhus plant.

The untoward reactions that have been observed to follow the intramuscular administration of ivy preparations are erythema and induration of the area receiving the injection, accentuation of itching, urticaria, multiforme erythema, dyshidrosiform dermatitis of the hands, and marked brawny edema of the sites of the existing dermatitis. These reactions have been interpreted as a dermal combined with an epidermal reaction. In

patients who developed a hematogenous dermatitis due to the poison ivy extract it was my impression that the course of the eruption was appreciably lengthened and the discomfort accentuated.

In summary, no significant differences in the rate of healing could be

Fig. 1. Results of patch tests on author's arm with commercial poison ivy extracts. Only three brands were sufficiently potent to elicit a positive patch reaction.

noted in the two series and the course was never aborted even when the injections were given within the first forty-eight hours after exposure to the plant. Judging both the poison ivy injection series and the control series by the same clinical criteria for cure, the average time required per case was approximately thirteen days in both series.

DERMATITIS-PRODUCING POTENCY OF COMMERCIAL POISON IVY EXTRACTS

An interesting observation was made concerning the dermatitis-producing potency of commercially purchasable ivy preparations to be given intramuscularly or orally. Figure 1 demonstrates the astonishing fact that

despite the high degree of the author's poison ivy sensitivity only three of eight brands of ivy extract gave a positive patch reaction on the author's arm on one occasion. Repeating the same procedure on other occasions it was found that most of the commercial extracts produced feeble reactions when applied as patch tests on subjects highly allergic to the poison ivy plant. These results indicate purchasable poison ivy preparations vary widely in their potency to produce skin reactions and some contain an insufficient quantity of allergen to elicit a positive reaction even in highly sensitive subjects. This may explain why only a few patients are made worse by the injection of these extracts and, of course, the negligible quantity of dermatitis-producing agents might well render these ineffective in treatment, provided one accepts the thesis that specific therapeutic effect and specific skin reaction are due to the same allergenic constituents. It is, however, conceivable, though not yet proved, that therapeutic efficacy and production of skin reaction are not necessarily based on identical allergenic agents.

PRESENT STATUS OF SPECIFIC TREATMENT

Intramuscular injections of poison ivy extracts are in general use today chiefly because of the recommendation of this procedure by Strickler and the enthusiastic reception it received. The rationale for the use of specific allergens for treatment is based on the principle of specific hyposensitization. This principle may be applicable to certain infectious diseases. For example, vaccination with cowpox virus early in the course of smallpox is thought by some to abort or to favorably modify the disease.

However, Stevens[11] in an excellent summarizing review states that "the data offered in the literature are not convincing in regard to the phylactic value of treatment with antigens of ivy orally or parenterally." He states further that "many patients are made worse because severe reactions occur when large doses of extracted solids are injected, and since the practice is not in conformity with theory, it is believed that the treatment of acute ivy rashes either parenterally or orally with ivy extracts should be vigorously discouraged." Both Shelmire's[10] experiments and the present results tend to support these statements.

THE COURSE OF IVY DERMATITIS WHEN NO INJECTIONS OF SPECIFIC ALLERGENS ARE ADMINISTERED

Before giving credit to a therapeutic procedure, the natural course of ivy dermatitis without that measure must be understood and taken as a base line for comparison. We know that rhus dermatitis is a self-limited disorder of relatively short duration, and healing occurs without therapeutic assistance. Several basic factors appear to determine the course and duration in the individual case. One of these is an unknown, individual variability. Some people overcome contact dermatitis much more speedily than one anticipates (within a few days), while some persons consistently

require a lengthy period for healing (several weeks). Moreover, it can be shown that, experimentally, when large amounts of poison ivy oleoresin contact the skin, the resulting dermatitis is more intense and the course longer than when smaller amounts are used on the same individual. It is also established that the subjective symptoms are more distressing when larger areas of the skin surface are involved. Thus a patient may tolerate a few patches of dermatitis venenata but be most miserable when the dermatitis involves larger areas of the integument. If certain skin sites have repeatedly been the seat of rhus dermatitis, they may exhibit a higher degree of allergic response than other areas in the same individual and of course people vary widely in their degree of hypersensitivity to the rhus plants. Those who have acquired a high degree of allergic sensitivity to rhus usually respond to exposure with reaction of longer duration than those possessing lower degrees of sensitivity. In addition, the subjective reaction to rhus dermatitis depends on individual variations similar to the variation of pain tolerance. Lastly, the discomfort in ivy dermatitis is not continuous but comes in waves of varying severity or intensity and duration.

SUMMARY

The present results in the employment of intramuscular injections of a potent brand of poison ivy extract (Lederle) in the treatment of acute poison ivy dermatitis did not confirm the claims of Strickler and others who introduced and popularized this procedure. The itching, burning and other discomfort did not disappear or become lessened in twenty-four to forty-eight hours following the first injection in any of the treated patients. When both series were appraised by the same clinical criteria for cure, the average time required for healing was the same in the group treated with ivy injections as in the control series.

Based on these results it is the author's opinion that poison ivy extract is contra-indicated for the treatment of acute rhus dermatitis. The procedure has not stood the test of time and has often been observed to do harm. The fundamental basis for phylactic therapy is unsound.

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FOOD ALLERGY IN DOGS

RALPH POVAR, D.V.M.
East Providence, Rhode Island

SUPERSENSITIVITY to food has been demonstrated in dogs affected with eczema.[1,4,5] Also the allergic origin of angioneurotic edema, due to foods, was ascertained as early as 1922.[3] In my practice, eight cases have been observed in dogs where food allergy could be established as the cause of serious disease.

Three of these cases concern urticaria. In two of these, eggs could be ascertained as the causative agent by elimination experiments. In the third dog, the supersensitivity was caused by commercial baked dog food (kibbles).

In addition, five cases of hemorrhagic colitis were seen, one of them lethal. One of the cases was complicated by chronic eczema. Clinical cure could be obtained in three cases by elimination of horse meat from the diet, and a fourth one by that of kibble. The fifth animal died before the materia peccans could be ascertained. This animal was fed on beef and kibbles. The post-mortem studies of this dog showed acute colitis with hemorrhage and thrombosis of underlying blood vessels.

Six out of eight animals involved were pure bred.

As several of the animals affected with hemorrhagic colitis showed infestation with intestinal parasites, it may be worth while investigating[5] whether parasites may have something to do with making the intestinal wall more permeable for antigens.

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This is an abstract of a paper read at the annual meeting of the American College of Allergists, San Francisco, California, 1946. A more detailed account will appear in a veterinary journal.

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and a wheal about 1.5 inches in diameter with pseudopods appeared at the site of the injection. Seven months later a similar test also resulted in a wheal. Subcutaneous injection of 1 c.c. of the vaccine resulted in local redness and induration and a rectal temperature of 100.4° F. Two days later 2 c.c. of the vaccine was injected and this was followed by reddening and induration for twelve hours. None of the intradermal or subcutaneous injections reproduced the purpura which was observed following the initial injection of the vaccine. The authors discuss the reasons for excluding thrombocytopenia as the mechanism for the purpura in this case and believe that the only explanation for the hemorrhagic tendency here appears to be capillary damage due to the liberation of histamine-like substances which are known to increase vascular permeability in shock and other anaphylactic conditions. They state that it is not surprising that purpura could not be reproduced by repeated injections of the vaccine, for rarely does anaphylactoid purpura recur in the same patient. Twenty other children inoculated with pertussis vaccine from the same lot as the reported patient in no instance developed purpura or any other anaphylactoid manifestation.

THE CHEMICAL AND IMMUNOLOGIC BASIS OF ORAL POLLEN PROPEPTAN THERAPY IN HAY FEVER

ERICH URBACH, MD., F.A.C.A., GEORGE JAGGARD, B.S., and DAVID W. CRISMAN, V.M.D.
Philadelphia, Pennsylvania

(Continued from March-April issue.)

Experiment 4.—Guinea pigs were allergized to dwarf ragweed pollen by subcutaneous injection of 5 per cent dwarf ragweed pollen extract precipitated with one per cent alum. Forty-five days later the following treatment was instituted.

Treatment: Five intravenous injections of dwarf ragweed digest at ten-minute intervals:

Injection 1.—Pollen digest representing 1.0 mg. soluble nitrogen—No reaction.
Injection 2.—Pollen digest representing 2.5 mg. soluble nitrogen—No reaction.
Injection 3.—Pollen digest representing 5.0 mg. soluble nitrogen—Bristling.
Injection 4.—Pollen digest representing 10.0 mg. soluble nitrogen—Bristling.
Injection 5.—Pollen digest representing 20.0 mg. soluble nitrogen—Bristling.

Two hours later: Inhalation of shock dose of five per cent dwarf ragweed pollen for twenty minutes:

Reaction: Slight diaphragmatic breathing.

Animals killed two hours after bronchial shock dose:

Schultz-Dale test—Positive.
Lung perfusion test—Very weakly positive.

Animals which were killed six hours after the bronchial shock dose exhibited negative Schultz-Dale test and negative lung perfusion test.

Experiment 4 demonstrates that skeptophylactic intravenous injections of pollen propeptan afford effective protection against bronchial shock dose.

Experiment 5.—Guinea pigs were allergized to dwarf ragweed pollen by subcutaneous injection of 2.0 c.c. of 5 per cent dwarf ragweed pollen extract, precipitated with 1 per cent alum. Fifty-five days later the following treatment was instituted.

Treatment: Inhalation with 10 per cent dwarf ragweed digest for thirty minutes —No reaction.

Two hours later: Intravenous shock dose of 5 per cent dwarf ragweed pollen extract:

Injection 1.—1 M.L.D.—No reaction.
Injection 2.—2.5 M.L.D.—Bristling.
Injection 3.—5 M.L.D.—Bristling and diaphragmatic breathing.
Injection 4.—10 M.L.D.—Bristling.
Injection 5.—20 M.L.D.—Bristling.

Animal killed two hours after last shock dose:

Schultz-Dale—Negative (Fig. 8).
Lung perfusion test—Negative (Fig. 9).

Experiment 5 shows that inhalation of ragweed propeptan for thirty minutes de-allergizes the entire organism of a highly sensitized animal to such a point that it can tolerate twenty M.L.D. by the intravenous route. De-allergization is demonstrated by the negative Schultz-Dale and lung perfusion tests (Figs. 8 and 9).

Experiment 6.—Guinea pigs were allergized to dwarf ragweed pollen by subcutaneous injection of 2.0 c.c. of 5 per cent dwarf ragweed extract precipitated with 1 per cent alum. Fifty-five days later the following treatment was instituted.

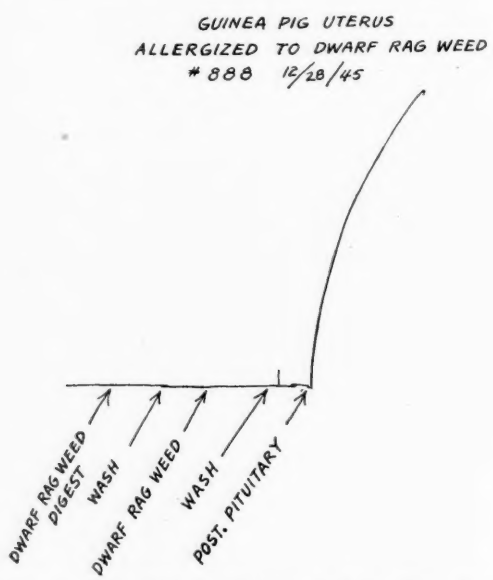

Fig. 8. Schultz-Dale test performed upon the uterus of a guinea pig allergized to dwarf ragweed pollen by subcutaneous injection of dwarf ragweed pollen extract precipitated with alum. Following a treatment of inhalation of dwarf ragweed pollen digest (dwarf ragweed pollen propeptan), the animal was able to tolerate a twenty times minimal lethal intravenous shock dose of dwarf ragweed pollen extract. The animal was killed two hours after the last injection. There was no reaction upon the addition of dwarf ragweed pollen digest or dwarf ragweed pollen extract, indicating the absence of antibodies.

Treatment: Inhalation of 10 per cent dwarf ragweed digest for thirty minutes —No reaction.

Two hours later: Shock inhalation dose of 5 per cent dwarf ragweed, exposure for thirty minutes—Slight bristling and diaphragmatic breathing.

Two hours later: Animal killed:

Schultz-Dale test—Positive.
Lung perfusion test—Negative.

Animals killed six hours after shock inhalation dose showed the same results, i.e., positive Schultz-Dale and negative lung perfusion tests.

Experiment 6 shows that inhalation of ragweed propeptan protects highly allergized guinea pigs against bronchial shock dose. However, while the bronchial antibodies are neutralized (satiated), those of the uterus are not.

Experiment 7.—Guinea pigs were allergized to dwarf ragweed pollen by subcutaneous injection of 2.0 c.c. of 5 per cent dwarf ragweed pollen extract precipitated with 1 per cent alum. Fifty days later the following treatment was instituted.

Treatment: By mouth, 5 mg. of soluble nitrogen of dwarf ragweed propeptan plus 0.2 gm. of glycyrrhiza plus 2.0 c.c. of water.

Forty-eight hours later: Intravenous shock doses of dwarf ragweed pollen at five-minute intervals:

Shock dose 1.—1 M.L.D.—No reaction.
Shock dose 2.—2.5 M.L.D.—No reaction.
Shock dose 3.—5 M.L.D.—No reaction.
Shock dose 4.—10 M.L.D.—No reaction.
Shock dose 5.—20 M.L.D.—Slight reaction, bristling.

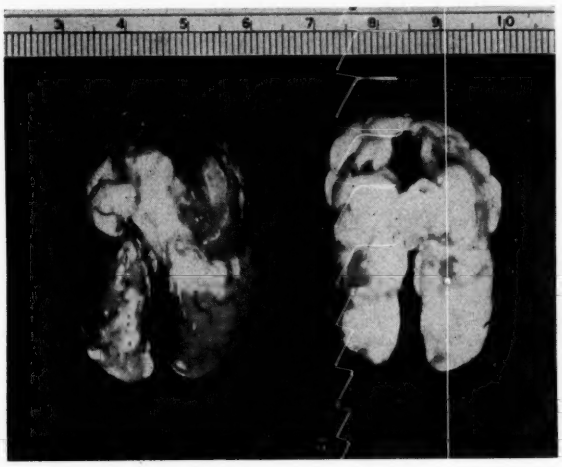

Fig. 9. Lung perfusion test performed upon the lung of a guinea pig allergized to dwarf ragweed pollen by subcutaneous injection of dwarf ragweed pollen extract precipitated with alum. Following a treatment of inhalation of dwarf ragweed pollen digest (dwarf ragweed pollen propeptan), the animal was able to tolerate a twenty times minimal lethal intravenous shock dose of dwarf ragweed pollen extract. The animal was killed two hours after the last injection. The lung (left) showed no inflation, indicating the absence of antibodies. A control lung of a non-allergized animal of the same weight (right) showed a negative reaction in the lung perfusion test.

Animal killed two hours after last shock dose by blow on the head:
Schultz-Dale test—Negative.
Lung perfusion test—Positive.

In animals killed six hours after last shock dose, both tests were negative. In those killed twelve hours after last shock dose the Schultz-Dale test was negative, but the lung perfusion test positive. When animals were killed twenty-four hours after last shock dose, both the Schultz-Dale test and the lung perfusion test were positive. However, in about 30 per cent of these experiments the guinea pigs would tolerate only ten M.L.D. and some animals exhibited marked diaphragmatic breathing even when receiving five M.L.D.

Experiment 7 demonstrates that oral administration of pollen propeptan protects only a fair percentage of animals against twenty M.L.D. of the antigen. However, in those cases where satisfactory protection was achieved, both uterus and lung were found to be free of antibodies six hours after administration of the last shock dose.

Experiment 8.—Guinea pigs were allergized to dwarf ragweed pollen by subcutaneous injections of 2.0 c.c. of 5 per cent dwarf ragweed extract precipitated with 1 per cent alum. Forty-six days later the following treatment was instituted.

Treatment: Oral administration of 20 mg. of soluble nitrogen of dwarf ragweed digest plus 0.2 gm of glycyrrhiza plus 2.0 c.c. of water.

Sixty-six hours later: Inhalation shock dose of dwarf ragweed pollen, 5 per cent for thirty minutes—Bristling and diaphragmatic breathing.

Twenty-four hours later: Oral administration of 20 mg. of soluble nitrogen of dwarf ragweed digest, glycyrrhiza and water.

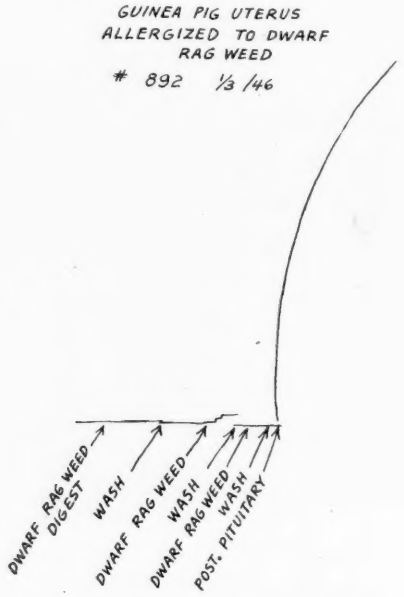

Fig. 10. Schultz-Dale test performed upon the uterus of a guinea pig allergized to dwarf ragweed pollen by subcutaneous injection of dwarf ragweed pollen extract precipitated with alum. The animal was treated with a series of oral administrations of dwarf ragweed pollen digest (dwarf ragweed pollen propeptan), followed by bronchial exposure to a pollen shock dose. The animal tolerated a ten times minimal lethal intravenous shock dose of pollen extract given two hours after the last inhalation shock dose. The animal was killed immediately after the intravenous shock dose. There was no reaction to dwarf ragweed pollen digest or dwarf ragweed pollen extract, indicating the absence of antibodies.

After two hours: Inhalation shock dose of dwarf ragweed pollen 5 per cent for thirty minutes—Bristling and diaphragmatic breathing.

Twenty-four hours later: (Same as previous twenty-four hours).

Twenty-four hours later: (Same as previous twenty-four hours).

Two hours after the last inhalation shock dose: Animal killed;

Schultz-Dale test—Negative.

Lung perfusion test—Negative.

If the animals were killed after six hours, the Schultz-Dale test was positive, the lung perfusion test negative.

Experiment 8 shows that temporary de-allergization is achieved (negative Schultz-Dale and lung perfusion tests), when oral administration of pollen propeptan is followed by bronchial exposure to a pollen shock dose, and the procedure is repeated three times at twenty-four-hour intervals.

Experiment 9.—Same procedure as in Experiment 8 except that an intravenous shock dose of dwarf ragweed pollen was given two hours after the last inhalation shock dose.

Shock dose 1.—2.5 M.L.D.—No apparent reaction.
Shock dose 2.—5 M.L.D.—No apparent reaction.
Shock dose 3.—10 M.L.D.—Very little bristling.

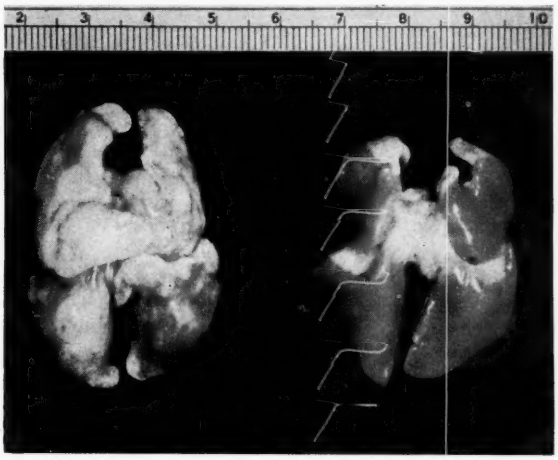

Fig. 11. Lung perfusion test performed upon the lung of a guinea pig allergized to dwarf ragweed pollen by subcutaneous injection of dwarf ragweed pollen extract precipitated with alum. The animal was treated with a series of oral administrations of dwarf ragweed pollen digest (dwarf ragweed pollen propeptan), followed by bronchial exposure to a pollen shock dose. The animal tolerated a ten times minimal lethal shock dose of pollen extract given two hours after the last inhalation shock dose. The animal was killed immediately after the intravenous shock dose. The lung (left) showed no inflation, indicating the absence of antibodies. A control lung of a non-allergized animal of the same weight (right) showed a negative reaction in the lung perfusion test.

Animal killed immediately after the last intravenous shock dose:

Schultz-Dale test—Almost negative (Fig. 10).
Lung perfusion test—Slightly positive (Fig. 11).

However, when six hours after the last inhalation shock dose 2.5 M.L.D. were given intravenously, the animal presented diaphragmatic breathing, and died in twelve minutes when ten M.L.D. were injected. The Schultz-Dale test was positive and lung was inflated.

Experiment 9 demonstrates that animals treated with pollen propeptans by the oral route and followed by bronchial exposure to pollen are given temporary protection against ten M.L.D., administered intravenously.

Experiment 10.—Guinea pigs were allergized to dwarf ragweed pollen extract precipitated with 1 per cent alum. Fifty-three days later the following treatment was instituted.

Treatment: Skeptophylatic inhalation of 5 per cent dwarf ragweed pollen extract 5 per cent as follows:

10-28-45—10 a.m. Time of exposure, 30 seconds—No reaction.
10-28-45— 4 p.m. Time of exposure, 60 seconds—No reaction.
10-29-45—10 a.m. Time of exposure, 1.5 minutes—No reaction.
10-29-45— 4 p.m. Time of exposure, 3 minutes—Bristling and diaphragmatic breathing.
10-30-45— 8 a.m. Time of exposure, 3.5 minutes—Bristling and diaphragmatic breathing.
10-30-45— 2 p.m. Time of exposure, 5 minutes—Bristling and diaphragmatic breathing.

Inhalation shock dose of dwarf ragweed pollen:
10-30-45— 4 p.m. Time of exposure, 30 minutes—10 per cent dwarf ragweed pollen extract.
Reaction: Bristling and marked diaphragmatic breathing. Two hours after the bronchial shock dose the animal was killed. Schultz-Dale test—positive. Lung perfusion test—strongly positive.

If animals of this group were sacrificed six hours after the bronchial shock dose, the Schultz-Dale test was again positive but the lung perfusion test negative.

Experiment 10 demonstrates that skeptophylactic bronchial exposure to whole pollen gives moderate protection against bronchial pollen shock dose, satiating temporarily the bronchial antibodies but not those of the uterus.

Experiment 11.—Guinea pigs were allergized to dwarf ragweed pollen by subcutaneous injection of 5 per cent dwarf ragweed extract precipitated with 1 per cent alum. Forty-seven days later the following treatment was instituted.

Treatment: Oral administration of 5.0 mg. of soluble nitrogen of dwarf ragweed pollen and 7.5 c.c. of water and 0.02 gm. of glycyrrhiza, daily for three consecutive days. No reaction to oral administration of pollen.

Two hours after the last oral treatment: An inhalation shock dose of dwarf ragweed pollen extract 10 per cent for ten minutes. Moderate reaction, bristling and diaphragmatic breathing.

Animal killed two hours after shock dose:
Schultz-Dale test—Positive.
Lung perfusion test—Strongly inflated.

Experiment 11 shows that whole pollen of dwarf ragweed administered orally gives a moderate degree of protection against a bronchial shock dose.

Experiment 12.—Guinea pigs were allergized to dwarf ragweed pollen extract by subcutaneous injection of 2 c.c. of 5 per cent pollen extract precipitated with 1 per cent alum. Fifty days later the following treatment was instituted.

Treatment: By mouth, 5 mg. of soluble nitrogen of cocklebur digest, 0.2 gm. of glycyrrhiza plus 2 c.c. of water.

After forty-eight hours: Shock doses of dwarf ragweed pollen, 5 per cent extract, intravenously:
Shock dose—1 M.L.D.—Animal died in six minutes with asthmatic symptoms.
Schultz-Dale test—Positive.
Lung perfusion test—Positive.

Experiment 12 demonstrates that nonspecific pollen propeptans do not protect sensitized animals at all.

DISCUSSION

Guinea pigs can always be strongly allergized by a subcutaneous injection of 2 c.c. of an aqueous extract of pollen precipitated with alum. This mixture insures slow absorption of the antigen. Sensitization is achieved somewhere between the forty-fifth and fifty-fifth day, provided the animal be kept on an acid diet.

Anaphylactic death will invariably follow intravenous administration of the shock dose. When the shock dose is administered by the bronchial route (in a specially constructed inhalation chamber), the overwhelming majority of animals will exhibit severe or deadly manifestations of anaphylaxis.

We also succeeded in allergizing guinea pigs by the bronchial route, whereupon these animals presented typical symptoms of bronchial asthma but no outright manifestations of anaphylaxis. In other words, we were able to induce the same symptoms in experimental animals as we so commonly encounter in human beings. This again refutes the very foundation of the concept of atopy which claims that "atopic" diseases, such as asthma, can occur only in human beings which are subject to hereditary influences. These experiments are more fully discussed in a separate paper.[8]

Group A comprises Experiments 3 and 4, in which highly sensitized animals were protected against twenty minimal lethal doses of pollen by skeptophylactic intravenous administration of pollen propeptans, i.e., by mounting doses of pollen digest given five times at ten-minute intervals. The fact that both the Schultz-Dale and the lung perfusion tests were negative indicates that the protection is attributable to neutralization (satiation) of the cellular antibodies. We call this form of immunologic protection "de-allergization," in contradistinction to "hyposensitization," in which both the cellular and the humoral antibodies are greatly increased in number (Urbach and Gottlieb[5]).

When the shock dose was administered intravenously, both the Schultz-Dale and the lung perfusion tests were negative two hours after the shock dose; however, when the animals were exposed to the latter by the bronchial route, it took six hours for the cellular antibodies in both the uterus and lung to be neutralized. This may be explained by the fact that, in the latter instance, it takes a longer time for the antigen to come into contact with the cellular antibodies.

In Group B (Experiments 5 and 6), treatment consisted of exposure to 10 per cent ragweed propeptan for thirty minutes in the inhalation chamber. The animals were able to withstand twenty M.L.D., injected intravenously, and the Schultz-Dale and lung perfusion tests were negative. Bronchial exposure to the shock dose was tolerated by the animals, but even after six hours the Schultz-Dale test was positive, indicating that not enough antigen had been absorbed to neutralize the antibodies of the distant shock organ. This, as we shall see below (Group C), differs from the findings in experiments where the antigen is given by mouth.

In Group C (experiments 7 and 8) the animals received pollen propeptan by mouth for protective purposes. Here again the vast majority was able to tolerate ten to twenty M.L.D. After two hours the Schultz-Dale test was negative, the lung perfusion test positive. After six hours both tests were negative. Twelve hours after administration of the multiple

minimal lethal dose, conditions were the same as those prevailing after two hours. After twenty-four hours both tests were positive. Oral administration of pollen propeptan, followed by bronchial exposure to the shock dose, repeated three times at twenty-four hour intervals, resulted in temporary de-allergization for the first two hours; after six hours the Schultz-Dale test became positive.

Why animals receiving pollen propeptan orally should, at first and then again later, give a positive lung perfusion test may perhaps best be explained by the fact that the lung contains a relatively greater number of antibodies, and that these are consequently more difficult to neutralize than those of the uterus.

Animals (Experiment 9) which were given pollen propeptan orally, and which then received a bronchial shock dose and lastly (two hours later) an intravenous injection of ten M.L.D. of pollen tolerated the latter almost without symptoms. At the same time the cellular antibodies in the uterus and lung were neutralized, as evidenced by the negative Schultz-Dale and lung perfusion tests. However, when the intravenous dose was administered six hours after the bronchial shock dose, all the animals died in anaphylactic shock.

In Group D (Experiment 10) the animals were treated with pollen extract instead of pollen digest. In Experiment 10 we subjected the animals to skeptophylactic inhalation of pollen extract, beginning with thirty seconds and gradually increasing the exposure to five minutes. While the animals withstood ten minutes of pollen inhalation, the Schultz-Dale test and the lung perfusion test were both positive. When treatment was begun with a three-minute exposure, the animals exhibited extremely severe symptoms of anaphylaxis in response to a five-minute inhalation period which followed the first exposure after a brief interval.

Oral administration of the whole pollen (Group E, Experiment 11) was found to provide a fair therapeutic result, but here again the reactivity of uterus and lung was strongly positive.

In Group F we endeavored to determine whether animals allergized to ragweed pollen could be protected by nonspecific pollen propetan, e.g., cocklebur pollen propeptan. Without exception, these animals died following the first minimal lethal dose.

Lastly we should like to state that similar extensive experiments as with dwarf ragweed propeptan were made with cocklebur propeptan and timothy propeptan. Since the results were virtually identical with those observed in the series of experiments with ragweed pollen propeptan, we feel that they do not warrant detailed discussion.

SUMMARY

Pollen propeptans are pollen digests derived from the individual pollen through prolonged acid and alkaline digestion of the ragweed pollen group, and prolonged acid digestion of the grass pollen. While these preparations

are devoid of native protein, they do retain type-specific immunologic properties, as demonstrated by the positive passive transfer test (Prausnitz-Kuestner reaction) when pollen propeptan is substituted for the pollen proper.

In the extensive series of animal experiments, it was learned that grass pollen propeptans are most efficacious when the preparations contain some 80 per cent of proteoses and peptones. Ragweed and cocklebur propeptans, on the other hand, afford the maximal protection when these degradation components comprise no more than 50 to 55 per cent of the total preparation.

Intravenous, oral and bronchial administration of pollen propeptans, under appropriate conditions as to quantity and timing, can protect highly sensitized guinea pigs against as many as twenty minimal lethal doses. On the strength of the temporarily negative Schultz-Dale and lung perfusion tests exhibited by animals protected in this manner, the opinion is expressed that pollen propeptan therapy produces temporary neutralization of cellular antibodies, or, in other words, de-allergization rather than hyposensitization.

While administration of pollen propeptan causes at least a temporary de-allergization, that of whole pollen does not diminish the allergic reactivity of the chief shock organs, uterus and lung, as demonstrated by positive Schultz-Dale and lung perfusion tests.

The results of these investigations seem to constitute experimental confirmation of the therapeutic value of specific pollen propeptan therapy in hay fever in man.

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ASTHMA DUE TO ODOR OF URINE, FECES AND SWEAT

HEBER C. JAMIESON, M.B., F.R.C.P. (C), F.A.C.A.
Edmonton, Alberta, Canada

THE fact that asthma may result from the odor of food is well known. Feinberg and Aries[1] reported three cases of asthma from food odors. These attacks were caused by the odor of cooking foods. Horesh[2] described a case of a child in which the odor of white potato uncooked was responsible for such attacks. Ingested foods are known to produce asthma.

The literature seems to show no record of this affection caused by the end products of metabolism when excreted in the urine, feces or sweat. For that reason the following case is of interest.

CASE RECORD

A twenty-seven-year-old housewife complained that ever since returning from the hospital with her first baby, bottle-fed and at present four months old, she got attacks of wheezing and coughing every time she changed the wet diapers or when she washed them. These attacks came on in about two minutes and lasted for half an hour. Should the baby have a stool as well, the attacks were more severe. The information was also elicited that if there was passage of gas without urine or stool, she also had dyspnea, coughing and wheezing. As the history unfolded, it was learned that the smell of heavy perspiration gave similar distress. Aside from these causes, Limberger cheese or green cheeses produced a tightening in the chest with wheezing if they were on the table near her. Two other substances bothered her, the odor of rotting seaweed and the putrid smell of skunk cabbage.

As far as she knew, there was no allergy in the family.

Physical examination revealed no abnormality except on the numerous occasions when various substances were being tested. Then dyspnea was occasioned and rhonchi were present in the chest.

The possibility of baby powder, soap and the various articles used in the care of the baby was considered, but the usual tests eliminated them. On a visit to her home, the sniffing of dry diaper caused no trouble, but a wet diaper brought on a typical paroxysm. The urine was acid to litmus and there was no odor of ammonia.

The natural conclusion seemed to be that the aromatic or ethereal sulphates were responsible. These are some of the end-products of protein metabolism. A brief note on them is of importance. Sampson Wright[3] says:

"Some of the aromatic amino acids (tryptophane, tyrosine and phenylalamine) pass into the large intestine, where they undergo putrefactive change and are converted into indol, skatol and phenol. These substances are absorbed into the blood, carried to the liver, oxidized to indoxyl and

skatoxyl, conjugated with sulphate, and excreted in the urine as the so-called ethereal sulphate."

The patient was given test tubes containing the following separately: butyric acid, proprionic acid, indol and valeric acid. On separate occasions she inhaled the odors of each.

Typical attacks were produced by all but valeric acid. Skatol was next tested and gave the most severe and prolonged attack.

Fresh urine was shaken up with an equal amount of ether and separated. This was repeated three times. The urine so treated failed to cause any trouble.

Folin states that on a protein-rich diet of adequate caloric value, the amount of ethereal sulphate excreted in the urine is 0.19 gm., whereas on a similar adequate but protein-poor diet, the amount of ethereal sulphate is only 0.1 gm.

In view of this fact, fresh urine from a patient on a protein-poor diet was given to the patient to inhale. She complained of only a slight feeling of tightness in the chest.

An investigation of the effect of perspiration was carried out next.

Sampson Wright[3] states that there are two kinds of sweat glands in man:

"1. *Eccrine,* which are distributed over the body surface and secrete a dilute solution containing sodium chloride, urea and lactate (in exercise). Eccrine glands are most dense on the palms and soles, next on the head, and much less on the trunk and extremities.

"2. *Apocrine,* large glands found mainly in the axilla and round the nipples, and in the female on the labia majora and mons pubis. They form a secretion of variable composition and characteristic odor."

Howell says that there are present in this sweat ethereal sulphates of phenol and skatol.

Sweat was collected from the face and upper chest and from the axilla separately. The former was clear and with little odor. The latter was cloudy and had a heavy smell.

The patient was allowed to inhale from the test tube containing the sweat which was mostly from the chin. There was no reaction. When the axillary sweat was tried, a typical attack with dyspnea, coughing and wheezing occurred, and rhonchi were present on stethoscopic examination.

SUMMARY

A case of asthma is reported which was due to the ethereal sulphates, the aromatic end products of protein metabolism as excreted in the urine, feces and sweat. The attacks due to cheese were no doubt caused by the acid formed by the proprionic bacteria present in these foods.

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REAGINS: PRELIMINARY REPORT ON EXPERIMENTAL EVIDENCE IN SUPPORT OF A NEW THEORY OF THEIR NATURE

Immunochemical Studies of Reagin 1.

HYMAN MILLER, M.D., F.A.C.A.
Beverly Hills, California
and
DAN H. CAMPBELL, PH.D.
Pasadena, California

EVER since the publication of Prausnitz and Küstner[9] on local passive transfer in 1921 there has been general acceptance of the theory that some sort of antibody, now called reagin, is probably responsible for allergic reactions. Much speculation as to the immunological and chemical nature of reagin has followed.

Experimental work such as that of Coca and Grove[2] and of Loveless[5] has given us a good knowledge of the differences in properties between reagin and normal antibody. Thus we know that reagin as opposed to normal antibody seems to be more heat labile; that the ability to produce reagin appears to be inherited; that this does not preclude the ability in allergic individuals to produce normal antibody to the same specific antigen; that the duration of sensitization produced by reagin is relatively long; that reagin does not produce a precipitate with its specific antigen; that it sensitizes the human skin; and that it does not neutralize its specific antigen. All these differences lead to the speculation that reagin must differ chemically or physically from normal antibody.

Having these differences in mind, the authors have postulated that the production of reagin in the so-called allergic group of humans is the result of some hereditary factor which permits the individual to form incomplete or distorted antibodies, and that this process is probably due to some genetic lack or mutant analogous to that demonstrated by Beadle[1] as responsible for distorting or abbreviating the chain enzyme reactions in amino acid metabolism in the red bread mold (neurospora crassa).

Furthermore, it was postulated that since reagin cannot produce precipitate with its specific antigen it probably lacks sufficient combining groups to build up a lattice of antigen and antibody in conformity with Marrack's[6] "Lattice Theory." In the light of Pauling's[8] theory that a minimum of two combining groups on an antibody is necessary to build up such a lattice and that normal antibody probably has but two such groups, it was further postulated that reagin is probably an antibody with only one combining group, that is, a unipolar antibody.

The present investigation was undertaken to determine if by serologic

From the Gates and Crellin Laboratories of Chemistry of the California Institute of Technology, Pasadena, California.
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TABLE I. HYPERSENSITIVE REACTIONS TO EGG WHITE OF PERSONS FROM WHOM TEST SERUMS WERE OBTAINED.

Patient	Symptomatic	Skin Tests	Prausnitz-Küstner
D	Negative ?	3-plus	Plus—minus
G	Positive	Minus	Plus—minus
Z	Positive	4-plus	4-plus
S	Positive	4-plus	4-plus
Se	Positive ?	3-plus	Minus
H	Positive	4-plus	4-plus
A	Negative ?	4-plus	4-plus
Y	Negative ?	3-plus	Minus
Sa	Negative	Minus	Minus

means some confirmatory evidence might be obtained for this theory. Using the precipitative reaction between ovalbumin and rabbit antiovalbumin, experiments were set up to determine whether reagin from egg-sensitive individuals would produce quantitative effects on the amount of precipitate produced. It was originally thought that perhaps some sort of inhibition would be obtained. However, as will be seen in the following data the opposite was true in most instances, and the reagin serum actually produced an increase in the amount of precipitate.

METHODS AND MATERIALS

Although experimental conditions were purposely varied to some extent, all experiments were carried out in the following general manner.

The reagin serums or the control serums were added to a series of varying dilutions of ovalbumin, and after allowing the mixtures to stand for several hours, rabbit antiovalbumin serum was added. The precipitates were then centrifuged, washed with saline, and analyzed for protein by the Folin-Ciocaltéu method.[10]

Reagin.—The reagin serums were collected from several individuals, all but one of whom showed some evidence of hypersensitivity to egg white. (Table I.)

Consideration was given to the desirability of heating the serum to 56° C. in order to minimize any variation due to involvement of complement in precipitation,[3] but the possible effect of complement was much less than variations which were obtained with heated reagin serums in a few preliminary experiments.

Antigen.—The antigen was an ordinary preparation of ovalbumin which had been recrystallized three times and then lyophilized. The dilutions used in most experiments varied by a factor of 1.5 and were selected to include the zone of maximum precipitation and portions of antigen and antibody excess zones.

Antiovalbumin.—The antiovalbumin was taken from a large sample of rabbit serum which had been pooled and lyophilized. A stock solution of antiserum was made by dissolving 8.0 grams of dried material in 100 milliliters of distilled water. Such a solution contained approximately 2.0 milligrams of antibody protein per milliliter.

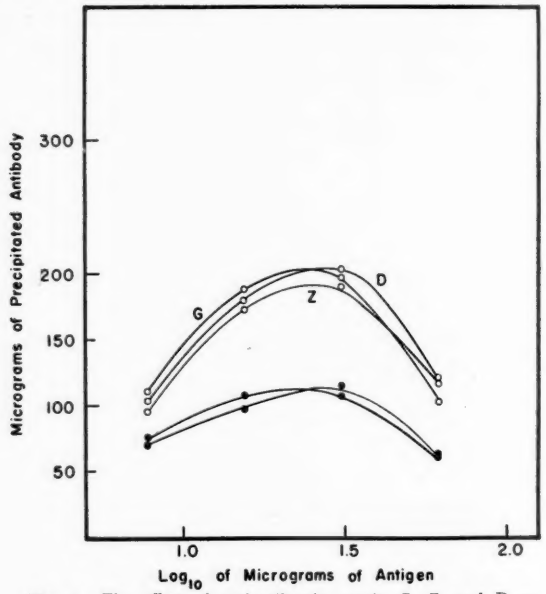

Fig. 1. The effect of antiovalbumin reagin G, Z, and D on the precipitation of ovalbumin and rabbit antiovalbumin. Solid circles are controls of saline and normal serum.

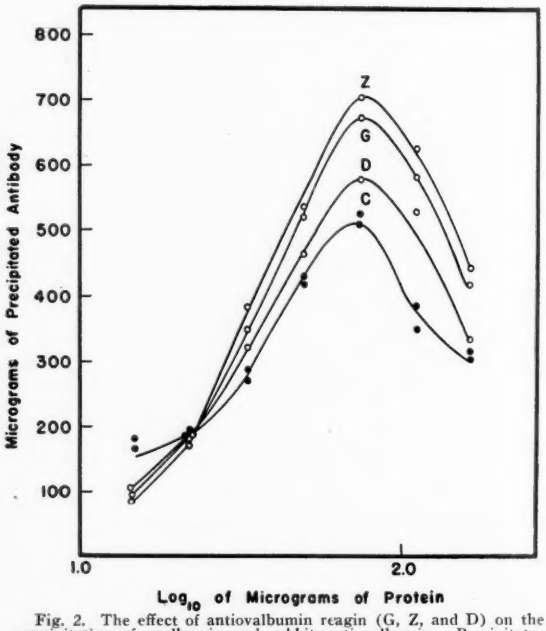

Fig. 2. The effect of antiovalbumin reagin (G, Z, and D) on the precipitation of ovalbumin and rabbit antiovalbumin. Precipitates analyzed at twelve hours.

Results.—Although the data of the following preliminary experiments clearly indicate that reagin has a significant effect upon an antigen-antibody precipitation system, the quantitative aspects must await refinements

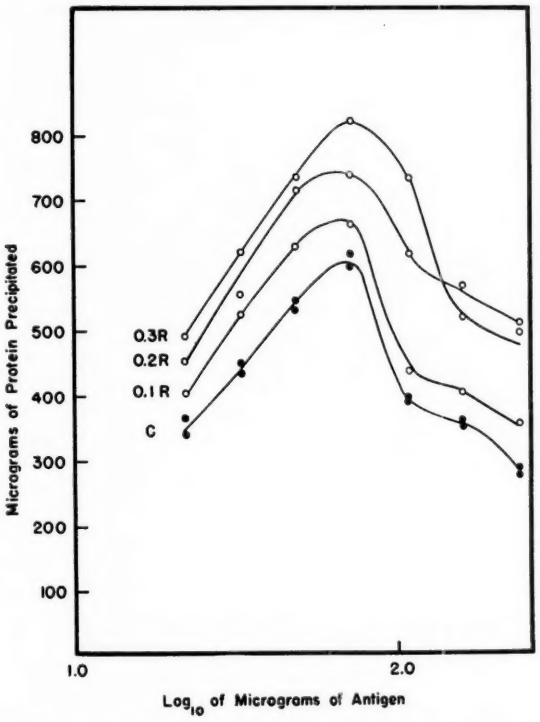

Fig. 3. The effect of various concentrations of antiovalbumin reagin (Z) on the precipitation of ovalbumin and rabbit antiovalbumin. Precipitates analyzed at forty-eight hours.

in methods. For example, the successive steps in antigen dilutions were too great to be certain of the point of maximum precipitation and therefore failed to detect such small shifts in the optimum zone as might have resulted from differences in antibody concentration. Furthermore, the observed experimental deviation of identical tests was as high as ± 30 micrograms of protein in the region of 500 micrograms total.

EXPERIMENTS

Experiment 1.—To 0.5 ml. samples of antigen which varied by a factor of 2.0 there was added 0.2 ml. of reagin from three different patients (G, D, and Z) and the mixture allowed to stand for two hours at room temperature. The two controls contained either 0.2 ml. of saline or 0.2 ml. of pooled normal human serum. To each tube 0.5 ml. of a 1:10 dilution of the stock anti-serum solution was then added. The precipitation reaction was allowed to proceed for two hours at room temperature and then about forty hours at 4° C.

This was the preliminary experiment which showed that instead of producing an inhibition of precipitation as was expected, reagin actually increased the amount of precipitate. The results are shown graphically in Figure 1.

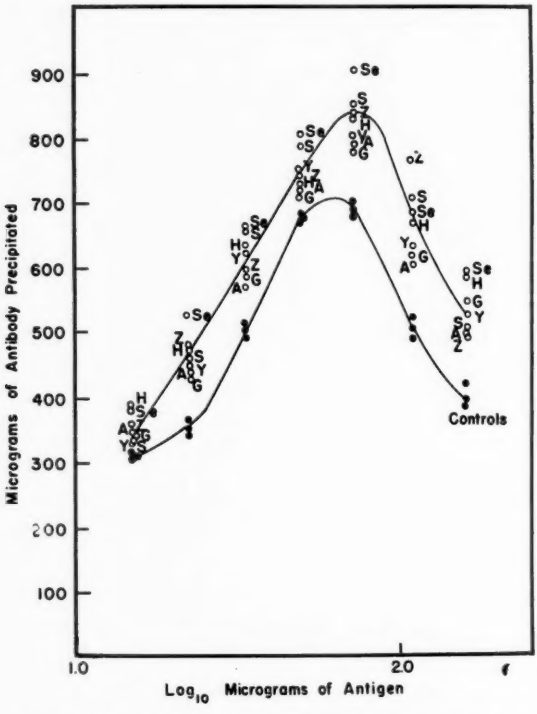

Fig. 4. The effect of antiovalbumin reagin (Se, S, Z, H, Y, A, and G) on the precipitation of ovalbumin and rabbit antiovalbumin. Precipitates analyzed at eighteen hours. Solid circles are controls, one of saline and two of serums from nonallergic persons.

Experiment 2.—The same reagins were tested in Experiment 2 but the precipitation system was slightly changed. Antigen dilutions were varied by only a factor of 1.5, the antiserum was diluted 1:2 and the precipitates analyzed twelve hours after the addition of antiserum.

The results, which are given in Figure 2, indicate that in addition to the production of an increase in the precipitate at the equivalence zone, the reagin tended to reduce the amount of precipitate in the antibody excess region. This effect is very similar to that obtained by Pappenheimer[7] and Heidelberger, Treffers, and Mayer,[4] who found that "weak" or univalent antibodies were formed against ovalbumin in horses during the early stages of immunization and that such antibodies decreased the amount of precipitation during the early phase of the precipitation reaction.

Experiments 3 and 5.—These two experiments were set up to measure the effect of varying the concentration of reagin serum. In Experiment 3 (Fig. 3) three different amounts of reagin (Z) were tested, namely, 0.1, 0.2, and 0.3 ml. of the undiluted serum. The effect obtained was chiefly that of increasing the amount

of precipitate with, perhaps, a slight tendency for the higher concentration (0.3 ml.) to cause a sharper fall in the curve in antibody excess region.

The fifth experiment was set up in essentially the same manner but with a

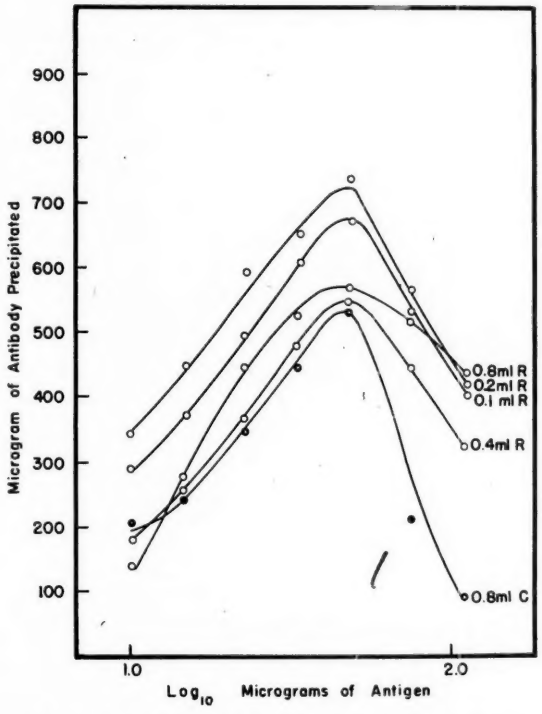

Fig. 5. The effect of varying the concentration of reagin (R) from 0.1 ml. to 0.8 ml. Control (C) was normal serum, and the precipitates were analyzed at forty-eight hours.

greater range of reagin concentrations. In order to have sufficient quantities of reagin serum, it was necessary to pool three samples, Z, G, and A. The results are given in Figure 5 and indicate that large amounts of reagin may actually tend to produce some inhibition of precipitation since the increase due to reagin was much less with 0.4 and 0.8 ml. amounts than with 0.1 and 0.2 ml. amounts.

Experiment 4.—The fourth experiment (Fig. 4) showed the effect of serum from seven different egg-sensitive patients. The amounts tested were 0.2 ml. samples in all cases, and the precipitates were analyzed at eighteen hours. Although there was considerable variation in the effect of the various serums, they all tended to increase the amount of precipitate. The curve drawn through the average values may be somewhat misleading since in certain instances there are distinct differences in the shape of the curves. However, it shows the average over-all effect and leaves no doubt that antiovalbumin reagin is incorporated in a precipitative system of ovalbumin and rabbit antiovalbumin. The actual values obtained for the ten different systems are given in Table II.

TABLE II. THE EFFECT OF ANTIOVALBUMIN REAGIN ON THE AMOUNT OF PROTEIN PRECIPITATED IN AN OVALBUMIN, RABBIT ANTIOVALBUMIN PRECIPITATIVE SYSTEM.

Added to system	Dilutions of antigen and corresponding amounts of antibody precipitated						
	14.97	22.45	32.95	49.38	74.07	110.10	166.06
Nothing	315	340	504	680	690	500	390
0.9% NaCl 0.2 ml.	304	333	505	670	708	488	423
Norm. Serum 0.2 ml.	336	362	488	685	684	539	389
H	389	480	622	717	830	670	589
S	308	471	663	792	848	717	505
Z	357	480	581	745	840	770	495
G	340	437	564	708	763	614	555
A	350	441	630	715	780	606	506
Se	385	530	663	800	912	696	593
Y	326	441	589	748	785	638	531

TABLE III. THE EFFECT OF ANTI-POLLEN REAGIN ON AN OVALBUMIN, RABBIT ANTIOVALBUMIN PRECIPITATIVE SYSTEM.

Material added	Antigen dilution and micrograms of protein precipitated					
	14.97	22.45	32.95	49.38	74.07	110.10
Normal serum 0.2 ml.	514	780	622	488	333	226
Reagin 0.2 ml.	547	717	598	480	329	239

Experiment 6.—The sixth experiment is a control with serum from a patient allergic to pollens only (Table III), showing that there was no increase in the amount of protein precipitated.

CONCLUSIONS

The foregoing experiments clearly show that serum from egg-sensitive individuals contains a type of antibody which attaches to egg albumin and is in some way incorporated in a specific precipitate formed by ovalbumin and precipitating antibody from rabbit antiserum. The data would indicate that the amount of combining reagin is considerable since, in some instances, 0.1 ml. of reagin serum increased the precipitated protein by 200 micrograms. The nature of the reagin antibody or antibodies must await further study but it would appear at present as though the peculiar serological activity of reagin was the result of a lack of a sufficient number of combining groups or groups too weak to afford the formation of insoluble complexes with its antigen, but that such antibodies will attach to a precipitating complex of strong antibody and antigen. It may be speculated that reagin represents the result of a distorted or incomplete antibody-forming mechanism, that is, that reagin is probably a unipolar antibody.

(References on Page 246)

SOME HELPFUL HINTS FOR MAINTAINING THE EFFICIENCY OF AEROSOL NEBULIZERS

ALVIN SELTZER, M.D.
Washington, D.C.

WITH the increased usage of aerosol nebulizers for vaporizing solutions of epinephrine, penicillin, et cetera, one often meets the problem of obstructions to the capillary tubes of the nebulizer caused by small particles of matter which may form in the solution being nebulized. These obstructions render the nebulizer useless, and the usual method of using

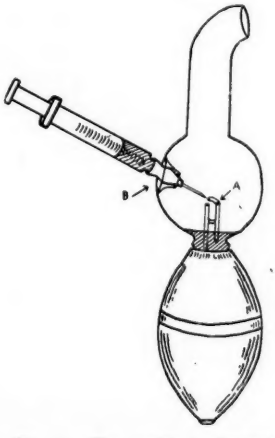

Fig. 1. The needle is inserted through the vent (B), which is usually kept closed by a plug, to force the indicated obstruction (A) out of the capillary tube into the main chamber of the nebulizer.

various types of cleaning solutions is most often not successful since these solutions will not get into the obstructed capillary tubes. Since the tubing is very delicate, it cannot stand much probing, and thus many of these obstructed nebulizers are thrown away as useless.

It is of great importance to inspect the nebulizers regularly to make sure that the capillary tubes are patent. Because of the fine nature of the spray, one can falsely be led to believe that nebulization is occurring, when actually all that is being produced is merely a hissing sound of air over an obstructed tube. This is particularly true in patients who are using the nebulizers at home. We have had several "failures" in asthmatics using 1:100 epinephrine spray, who were relieved when their nebulizers were cleared of obstructions.

From the Allergy Clinic, Regional Office, Veterans Administration, Washington, D. C.

In the first place, it is best to select a nebulizer which has a vent in the side. This vent is used to put the solution into the nebulizer, but it is also used to get at the tubing for cleaning purposes. The DeVilbiss No. 40 is a good example of this type. There are several types of nebulizers on the market which have no vent on the side, and the solutions are poured into the top of the vaporizer. These types, if obstructed, are very difficult to clean. Here, then, is a hint to manufacturers: all nebulizers should be arranged so that the tube which is not connected with the bulb will face the vent in the side of the nebulizer (Fig. 1). With this arrangement it is simple to keep the nebulizer free from obstructions.

The obstructions which occur always take place in the capillary tube which has no direct connection with the blast of air, and all the blowing of solvents through the nebulizer will not remove the obstruction, but will rather tend to wedge it more firmly into place. However, if a fine long needle is put on a small syringe filled with water, and directed through the vent in the side of the nebulizer, so that the point of the needle rests on the opening of the obstructed tube (Fig. 1), then a small squirt of water from the syringe will flush the obstruction out of the capillary tube into the main chamber of the nebulizer, where it can be readily washed out. This can be done in a few seconds without damage to the delicate tubes, and it restores the nebulizer to full efficiency.

Thus, one can see the value of using a nebulizer which allows access to the capillary tubes. The use of other types of nebulizers will result in shorter periods of use.

Penicillin Sensitivity

In view of the increasing reports of penicillin sensitivity, the following abstract, which appeared in *The Chemist and Druggist,* September 8, 1945, was furnished upon request, through the courtesy of the editor. The note on Sycosis Barbae was abstracted from the *British Journal of Dermatology and Syphilis.*

SYCOSIS BARBAE—The "British Journal of Dermatology and Syphilis" (May-June, 1945) records the successful use of a penicillin cream in cases of sycosis barbae. The formula for the cream base was:—

Distilled water	250 c. c.
Lanette Wax SX	50 gm.
Castor oil	50 c. c.

To this, an amount of 200 units of penicillin per gm. was added. In nineteen cases where the predominant organism was found to be a penicillin-sensitive strain of staphylococcus, the cream was used with benefit. In thirteen with a history of more than a year, six were cleared within an average of six weeks, and six others showed improvement within this period. Of the six patients with a history of less than a year, four were cleared in an average of two and a half weeks and one was improving over a period of five weeks.

Department of Clinical Pathology and Laboratory Procedures

THE WELTMAN REACTION AS A DIAGNOSTIC AID

L. O. DUTTON, M.D.
El Paso, Texas

WITH the advance of effective antibiotics useful in the treatment of respiratory infections that have in the past resisted other forms of therapy, it has become more important in the management of asthma to be able to differentiate between true allergic asthma and infectious bronchial asthma, or to be able to detect a low-grade infectious process which has been grafted on an original allergic asthma. Regardless of one's opinion as to the mechanics by which chronic infection of the respiratory passages complicates the asthmatic picture, it is desirable to detect such infection so as to institute treatment to overcome it. Such a differential diagnosis is by no means always easy, and any additional diagnostic procedure of value should be welcome.

In 1941 Dees[1] called attention to the value of the Weltman coagulation reaction in the diagnosis of the presence and degree of infection in allergic individuals. Although the conclusions reached in her paper were strikingly in support of its value, the test has gained little popularity. In view of the simplicity of the technique involved, it is surprising that this is so. This short communication is to call attention again to this valuable procedure. The technique of the test is simple, and the essential reagent is easily prepared and stable.

Quoting Dees' paper: "The technique of the test as described by Weltman is as follows: Ten dilutions of $CaCl_2 \cdot 6H_2O$ solutions ranging from 0.1 to 0.01 per cent are prepared from a stock solution of 10 per cent $CaCl_2 \cdot 6H_2O$. Five cubic centimeters of each of these solutions are measured into small test tubes which are numbered from one to ten to correspond with the dilutions. To each tube is added exactly 0.1 cubic centimeter of unhemolyzed serum. The contents of the tubes are thoroughly mixed and placed in their rack in a boiling water bath for fifteen minutes. They are then removed and the number of tubes in which coagulation is present is noted. Normal serum regularly coagulates in the first six tubes of the series in concentrations from 0.1 per cent through 0.05 per cent $CaCl_2 . 6H_2O$. In most instances there is turbidity in addition to flocculation in more than the first six tubes. This turbidity is not considered, however, in determining the end point of the test, since degrees of turbidity are difficult to estimate, are variable, and show no apparent relationship to findings in normal and pathologic states. The

values are expressed as a coagulation band corresponding to the number of tubes showing flocculation. For example, normal serum is said to have a coagulation band of six, or CB=6."

In the interpretation of the test, any reading below a coagulation band of six is indicative of some type of acute or chronic inflammatory process. The test is not subject to a great many variable factors, as are the white count and the sedimentation rate, and is to be interpreted identically in both children and adults.

In our laboratory, this test has become the most dependable single indicator of an inflammatory disease which we have at our disposal. The original article should be consulted, as it is an excellent presentation and is supplemented by a complete biography up to the date of its writing. This test is one that requires no elaborate apparatus nor complicated technique. It is quite applicable for use in a small laboratory and certainly deserves a wider use.

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(Continued from Page 223)

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(Continued from Page 242)

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Editorial

The opinions expressed by the writers of editorials in the ANNALS *are individual and do not necessarily represent the group opinion of the Board or of the College.*

A REMARKABLE MEETING OF THE NEW YORK ACADEMY OF SCIENCES

Though the New York Academy of Sciences likes to serve cocktails among the dinosaurs,* it is itself the least fossil organization imaginable. Its conferences on selected topics in biology are becoming an important feature in interscience relations. The attention of the readers of this journal previously was directed to a conference on allergy which was held on April 25 and 26. The most important aspects of the problem were presented in a series of papers of high academic level. They will be published *in extenso* in the *Annals of the New York Academy*. Two of the topics were of such immediate interest to the practicing allergist that they merit a few words of comment at this time.

Samuel Karelitz, Mt. Sinai Hospital of New York, presented the results of his work on serum sickness. Some of this work has been published in the *Journal of Immunology*, but its full impact came only to the fore at this meeting. As was already known from v. Pirquet and Schick, serum disease is not correlated with precipitating antibody (which may or may not be present in the serum of patients). In serum taken from patients three to twelve days after injection with equine antitoxin, Karelitz demonstrated a not-precipitating antibody demonstrable by passive transfer of generalized reaction, by local sensitization both to locally (intradermally) applied and to intravenously injected antigen, and by inverse passive sensitization. It is heat stabile (90 minutes 56°C. or 60 minutes 60°C.), and has a neutralizing effect, insofar that a properly balanced mixture of Karelitz' antibody and antigen (= equine protein) is nonreactive if introduced into the sensitized skin. It may be present for a considerable length of time; in one patient it could be demonstrated three years after serum treatment. The properties of the antibody of serum disease resemble those of the heat stabile, neutralizing antibody of pollinosis. In function, however, there is the thought-provoking difference, that the antibody of Karelitz induces sensitization, whereas the antibody of Cooke and Loveless is protective.

One session of this meeting was dedicated entirely to familial nonreaginic allergy. Milo G. Meyer from Michigan City, Indiana, reported on about 100 patients and Alan Johnston of Indianapolis on a smaller number of patients with assorted allergies. Edward T. Whitney of Boston reported on twenty patients with pruritus ani. (One important detail:

*In the famous Dinosaur Hall of the American Museum of Natural History.

he found that only those cases of pruritus which did not show signs of local changes represented familial nonreaginic allergy.) Thus, Coca's clinical syndrome of idioblapsis and the therapeutic effect of elimination of the causative allergens were confirmed from three independent sources. These clinical papers were complemented by a review of Locke on the correlation of familial nonreaginic allergy and susceptibility to common colds, and by a report by A. F. Coca on the results of sympathectomy in three desperate cases of idioblapsis (see May issue of the ANNALS).

A. J. W.

ASTHMA AS A CAUSE OF DEATH IN CHILDREN: REPORT OF A CASE.
Pedrero, José. (Muerte por asma en niño: reporte de un caso). Bol. Soc. cubana de pediat., 17:95-99, March 1945.

The author reports the case of a white boy, thirteen years old, who entered the hospital on August 8, 1942, at 5 a.m. because of an acute attack of asthma which had occurred suddenly a few hours before. The usual measures did not stop the increasing dyspnea; cyanosis appeared, and death occurred at 8:30 a.m. There was no autopsy.

Family History.—Father suffered from gastrointestinal allergy, especially to fish, marked by urticaria. A younger brother had died of anaphylactic shock after an injection of anti-tetanus serum.

Personal History.—Born at term, the child was breast-fed and had a normal development. In January, 1936, his adenoids were removed, and two months later he had his first attack of asthma, which was moderately severe with vomiting, and lasted some hours. From this time on, the attacks occurred every two or three weeks and increased in severity. In April, 1937, he had measles and, shortly after, urticaria lasting for several months.

In March, 1941, he came to the allergy department. He was then twelve years old and weighed 63 pounds. Intradermal tests were positive for oranges, spinach, white beans, chocolate; positive reactions to house dust, cat's hair, and wool. He was moderately positive to Staphylococcus albus, Streptococcus hemolyticus and Micrococcus catarrhalis. Instruction was given to avoid the allergic substances and a month later he had gained two pounds and had been free from attacks. After that he was not seen again, but his history indicated that the attacks had recurred and that he had had an attack of mumps a month and a half before his death.

Death caused directly by asthma used to be considered extremely rare and is probably rather unusual in proportion to the great frequency of asthma and other allergic diseases. Up to 1926 only eleven cases had been published, the majority of which were in adults. However, in 1928, Bivings reported a case in a child of ten months, and Waldbott cited one in a sixteen-months-old child. Thieme and Sheldon studied seven cases, of which two were children.

There are many theories as to the mechanism of death in asthma, none of which alone is sufficient to explain the individual cases. Among them are: inhibition of cardiac function, sudden myocardial insufficiency, toxemia, dehydration, et cetera. The author believes that dehydration and disturbances of acid base equilibrium may play a large part.

FALL GRADUATE INSTRUCTIONAL COURSE

The American College of Allergists announces its Fall Graduate Instructional Course in Allergy to be held under the auspices of the College of Medicine, University of Cincinnati, Cincinnati, Ohio, November 3-8 inclusive. Hotel headquarters will be at the Netherland Plaza.

The faculty consists of more than forty outstanding physicians and scientists from prominent medical centers and colleges in the United States and Canada.

Each course presents a complete, up-to-the-minute study of the entire field of allergy. The program covers fundamentals such as physiology, immunology, psychosomatics, and pathology; special allergies such as mold, food, bacterial, and physical; pharmacology of drugs used in the treatment of allergy; preparation of allergenic extracts; techniques of skin testing; and the determination of allergic history. Adequate consideration is given to specific diseases such as bronchial asthma, allergic bronchitis, bronchiectasis, Loeffler's syndrome, Ménière's disease, hay fever, and aural, ocular, vascular, joint and neuro allergy. There are also comprehensive symposiums on dermatologic and pediatric allergy.

The fee for the course is $100.00. The course has been approved by the Veterans Administration for the training of veterans under Public Law 346. There will be special bus service between the hotel and the Medical College.

Early registration is urged because the number of students may have to be limited due to the facilities of the hotels and the Medical College.

Make all reservations for the course and hotel accommodations directly with the secretary, Dr. Fred W. Wittich, 423 LaSalle Medical Building, Minneapolis, Minnesota. In making your reservation please state the exact time of your arrival and departure and whether you want a single room or wish to share one with another registrant. The number of single rooms is limited.

FACULTY

Harold A. Abramson, M.D., F.A.C.A., Assistant Professor of Physiology, Columbia University; Associate Physician in Allergy, Mount Sinai Hospital, New York, New York.

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Foster Kennedy, M.D., Professor of Neurology, Cornell University Medical College, New York, New York.

J. Harold Kotte, M.D., Assistant Professor of Medicine, Medical College, University of Cincinnati, Cincinnati, Ohio.

Hugh A. Kuhn, M.D., F.A.C.A., Hammond, Indiana.

Mary H. Loveless, M.D., F.A.C.A., Assistant Professor of Medicine, Cornell University Medical College, New York, New York.

John H. Mitchell, M.D., F.A.C.A. Assistant Professor, Department of Medicine, Director of Out-Patient Clinic, Ohio State University, Columbus, Ohio.

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Bela Schick, M.D., F.A.C.A. (Hon.) Clinical Professor of Pediatrics, College of Physicians and Surgeons, Columbia University; Pediatrician, Chief, Sea View Hospital, New York, New York.

A. B. Schwartz, M.D., Milwaukee, Wisconsin.

Howard L. Stitt, M.D., F.A.C.A. (Assoc.) Clinical Instructor, Children's Hospital; Medical College, University of Cincinnati, Cincinnati, Ohio.

Albert V. Stoesser, M.D., F.A.C.A., Clinical Professor of Pediatrics, University of Minnesota; Director of Allergy Clinics, University Hospital and Minneapolis General Hospital, Minneapolis, Minnesota.

J. Warrick Thomas, M.D., F.A.C.A., Graham-Thomas Clinic, Richmond, Virginia.

Leon Unger, M.D., F.A.C.A., Associate Professor, Department of Medicine, Northwestern University Medical School, Chicago, Illinois.

George L. Waldbott, M.D., F.A.C.A., Head of Allergy Department, Harper Hospital, Detroit, Michigan.

Charlotte Wiedemer, M.D., F.A.C.A., Instructor of Medicine, Medical College, University of Cincinnati, Cincinnati, Ohio.

Orval R. Withers, M.D., F.A.C.A., Associate Professor of Medicine, School of Medicine, University of Kansas, Kansas City, Kansas.

Fred W. Wittich, M.D., F.A.C.A., Managing Editor, Annals of Allergy, Minneapolis, Minnesota.

Roger P. Wodehouse, Ph.D., F.A.C.A. (Assoc.) Associate Director of Research in Allergy, Lederle Laboratories, Pearl River, New York

FALL GRADUATE INSTRUCTIONAL COURSE

PROGRAM

Monday, November 3, 1947

FUNDAMENTALS OF ALLERGY

8:30- 9:30	Registration.
9:30- 9:45	Address of Welcome, Dean Stanley Dorst.
9:45-10:30	"The Physiology of Allergy," Dr. Fred W. Wittich.
10:30-11:15	"Immunological Aspects of Allergy," Dr. Mary Loveless.
11:15-12:15	"The Clinical Significance of Recent Chemical Studies of Allergens," Dr. Harry S. Bernton.
12:15- 1:15	"Basic Principles of Allergy"—Moving Pictures, Dr. Bret Ratner.
2:15- 3:15	"Psychosomatic Factors in Allergy," Dr. John H. Mitchell.
3:15- 3:45	"Present Status of Antihistamine Drugs," Dr. Jonathan Forman.
3:45- 5:00	"Pharmacology of the More Important Drugs Used in Allergy," Dr. D. E. Jackson.
7:00	Informal Dinner—Speaker: Dr. Hal M. Davison.

Tuesday, November 4, 1947

FUNDAMENTALS OF ALLERGY

9:00- 9:30	"X-Ray in Allergy; Diagnosis and Treatment," Dr. Paul Moore.
9:30-10:30	"Bacterial Allergy," Dr. E. E. Ecker.
10:30-11:15	"Food Allergy," Dr. Hal M. Davison.
11:15-11:45	"Balanced Diet," Dr. William B. Bean.
11:45-12:30	"Elimination Diet,"Dr. Herbert J. Rinkel.
12:30- 1:15	"Physical Allergy," Dr. Harold A. Abramson.
2:15- 3:15	"The Preparation and Standardization of Extracts," Dr. Morris A. Kaplan.
3:15- 4:00	"Skin Testing: Technique and Interpretation," Dr. William F. Mitchell.
4:00- 4:30	"History Taking," Dr. J. Warrick Thomas.
4:30- 5:00	Demonstration, Dr. Charlotte Wiedemer.

Wednesday, November 5, 1947

RESPIRATORY ALLERGY

9:00- 9:45	"Pathology of Asthma," Dr. Milton G. Bohrod.
9:45-11:15	"Bronchial Asthma: Diagnosis, Management and Treatment," Dr. Leon Unger.
11:15-12:00	"Aerosol Treatment of Asthma," Dr. Harold A. Abramson.
12:00-12:30	"Bronchoscopy in the Treatment of Asthma," Dr. Howard L. Stitt.
12:30- 1:15	"Cardiac Asthma and Cor Pulmonale," Dr. J. Harold Kotte.
2:15- 3:15	"Allergic Bronchitis, Bronchiectasis and Loeffler's Syndrome," Dr. Vincent J. Derbes.
3:15- 3:45	"Allergic Rhinitis," Dr. French K. Hansel.
3:45- 4:15	"Aural Allergy," Dr. Hugh A. Kuhn.
4:15- 5:00	—"Ocular Allergy," Dr. A. D. Ruedemann.
8:00-10:00	Clinic.

FALL GRADUATE INSTRUCTIONAL COURSE

Thursday, November 6, 1947

HAY FEVER

9:00- 9:30 "Botany of Hay Fever Plants," Dr. Roger P. Wodehouse.

9:30-11:00 "Hay Fever: Diagnosis, Treatment and Management," Dr. George E. Rockwell.

11:00-11:45 "Pollen Respiratory Allergy with Negative Cutaneous Reactions," Dr. M. Murray Peshkin.

11:45-12:45 "Mold Allergy: Symptoms, Diagnosis and Treatment," Dr. Homer E. Prince.

12:45- 1:15 "Pollen Counts and Demonstration," Dr. Charlotte Wiedemer.

2:15- 3:15 "Vascular Allergy," Dr. Milton G. Bohrod.

3:15- 5:00 "Clinical Use of Histamine," Dr. Bayard T. Horton.

Friday, November 7, 1947

DERMATOLOGIC ALLERGY

9:00- 9:45 "Atopic Dermatitis," Dr. Stephan Epstein.

9:45-10:45 "Contact Dermatitis," Dr. Leon Goldman.

10:45-11:25 "Urticaria," Dr. R. F. Hughes.

11:25-12:20 "Soap and Other Detergents," Dr. Irvin H. Blank.

12:30- 1:30 "Drug Allergies," Dr. Ethan Allan Brown.

2:30- 3:00 "Joint Allergy," Dr. Bela Schick.

3:00- 4:15 "Neuro Allergy including Migraine," Dr. Foster Kennedy.

4:15- 5:00 "Unusual and Obscure Conditions of Allergies," Dr. C. R. K. Johnston.

Saturday, November 8, 1947

PEDIATRIC ALLERGY

9:00- 9:45 "Management of the Pre-Allergic Child," Dr. Bret Ratner.

9:45-10:30 "Characteristics of the Allergic Child," Dr. A. B. Schwartz.

10:30-11:45 "Special Problems in Treatment and Management of Asthma in Children," Dr. George Piness.

11:45-12:45 "Infantile Eczema," Dr. Albert V. Stoesser.

12:45- 1:30 "Gastro-intestinal Allergy in Children," Dr. Orval R. Withers.

On Tuesday, Thursday and Friday evenings from 8:00-10:00 p.m., there will be instructors in Parlors A and B, Netherland Plaza Hotel, so that if they desire, students may visit, ask questions and have informal discussions.

Speaker at Large and Director of Round Table Discussion, Dr. George L. Waldbott.

Progress in Allergy

HAY FEVER
A Review of the Literature of 1946

MORRIS A. KAPLAN, M.S., M.D., F.A.C.A.
and
NORMAN J. EHRLICH, M.S., M.D.,
Chicago, Illinois

Spain[105] summarized our problem in hay fever by stating, "While the concept of the hay-fever reaction may be simple, its explanation is not. Many questions remain to be satisfactorily answered. Such questions pertain to the allergic behavior of the victim, to the chemical structure of the pollen antigen with the assay of its activity, and to the nature of the allergic reaction which implements the hay fever condition, and upon which are based methods of specific diagnosis and treatment, both largely empirical. There is yet no satisfactory explanation as to why only 2.3 per cent of the population of the United States develop hay fever, despite the fact that all are equally exposed to pollen contacts." He continued by stating that, "To the worker in allergic problems, the preparation and standardization of pollen extracts is of prime importance; the lack of uniformity and agreement in these matters is disturbing."

BOTANY

Small and Small,[101] from a very comprehensive, extensive, and adequate survey of various regions in Southern California, concluded that Southern California had perhaps the greatest number and widest variety of hay fever-producing plants in the United States; however, the quantity of pollen contaminating the air of the cities was not very large. The ragweed and grass seasons, however, were much longer than elsewhere. Harsh,[53] in his report on pollinosis in Imperial County, California, and Yuma, Arizona, discussed the abundance of pollens, pollinating dates, relative pollinating ability, size of pollen grains, and pollen toxicity. Harsh suggested that the skin reaction of the patient should be considered first in relation to the abundance of the reacting species and then in relation to the amount of pollen produced and its bouyancy as indicated by the size of the grains. In Queries and Minor Notes,[86] a question was asked about the pollen content in Los Angeles. Durham notes that, during July, August, September, and October, the Western ragweed there was equal to about 2.5 per cent of that in Chicago. During March and November, there were small amounts of *Alternaria* and *Hormodendrum* molds, and grass and chenopod-amaranth pollens were less than ragweed, and a very small amount of sage. Bermuda grass was widely used in California for lawns. Targow[109] stated that the following ragweed species also were found in California: *Ambrosia psilostachya* and *Franseria acanthicarpa*. However, their pollen count was very low.

Bieberdorf and Hampton[13] discussed airborne fungi in the San Antonio, Texas, area, as ascertained from exposure plates and vaseline-coated slides. Mold spores were found on the plates and slides almost each day, and high counts were recorded during the entire survey. Nine genera made up 90 per cent of the molds encountered. *Hormodendrum* and *Alternaria* were highest in incidence by the plate method, whereas, in the slide studies, *Alternaria* and *Helminthosporium* were found most frequently. No definite seasonal trends of the individual molds was noted. Of 1,515

Dr. Ehrlich is an Associate Member of the American College of Allergists.

patients with proved allergic disease, 12.28 per cent showed definitely marked skin reaction to one or more molds, as compared to 0.012 per cent of 488 normal controls.

Larsen and Weller[65] reported that ragweed was appearing in Hawaii. Of 100 patients with positive skin tests, 30 per cent reacted to dust, 28 per cent to Bermuda grass, 20 per cent to algaroba, 30 per cent to amaranth, 12 per cent to Johnson grass, and 10 per cent to sugar cane. It was noted that the pollen count in this area varied with humidity, wind, temperature, and light. Also, there was an interrelation between these factors that caused sudden increase in the pollen count at varying times from 2 a.m. to 6 p.m.

Hyde and Williams[57] conducted a grass pollen survey near Cardiff, Wales, from June 15 to June 22, 1944. Four sets of slides were exposed. Two were impact slides attached in a vertical position to a weather vane and the other two were gravity slides in an apparatus similar to that described by Durham. The sites chosen for exposure were a patch of grassy vegetation and the top of a building. The slides were exposed for two-hour periods throughout the day and observations were made on sunshine, rain, wind direction, and wind velocity. These data were plotted on a graph and it was noted that all four graphs moved up and down in unison, with no apparent time lag between the ground and roof catch. A morning and afternoon rise was noted at both sites every day; however, the impact catch always was ten times greater than the gravity catch at each site. Highest counts were encountered following several hours of bright sunshine. Afternoon counts were relatively low on cloudy days. Variation in pollen counts were more marked on the ground than on the roof site and were closely related to the flowering of the principal grasses in the area. Low counts during hours of darkness were correlated with the total cessation of flowering during that period. It was concluded that there is a diurnal variation in grass pollen counts that can be correlated with the incidence of bright sunshine and with the flowering of neighboring grasses. The impact catch appeared to be a more sensitive index of grass pollen liberation than did the gravity method.

Hyde and Williams[57] also made studies at Cardiff on the incidence of *Alternaria* spores by counts, using the gravity slide method. They observed that *Alternaria* spores formed a normal and regular part of the annual spore rain at Cardiff and were present in the spring and summer, in greatest numbers during the months of June through September. During the late autumn and winter months, they virtually were absent. The slide collection during June through September totalled 646 spores in 1942 and 726 in 1943. The period of highest incidence coincided with that of the highest mean temperature. The catch during the summer months varied considerably from day to day. There seemed to be no relation between wind velocity and catch. On certain occasions, rainfall resulted in a temporary, although at times marked, diminution in the catch. Some figures were presented, comparing the daily catch in Wales with places in the Eastern United States. The authors expressed the opinion that the spores in Cardiff originated in cereals growing in the vicinity.

Boggs[15] reported on a patient with early spring hay fever, apparently due to the effect of pine pollen. Ordman[82] reported on fourteen patients with winter-spring hay fever and allergic conjunctivitis associated with cypress pollen sensitivity. He discussed the management of these patients in detail, beginning hyposensitization early in April and continuing until the middle of June.

Lima et al.,[67] stated that hay fever was unusual in Brazil, although the incidence of other allergic manifestations apparently was similar to that in other countries. Up to the time of their report, apparently only one case of hay fever had been reported—a Spanish patient. It might be significant that no incidence of typical hay fever had been reported among native Brazilians. Various opinions have been expressed to explain why pollinosis is rare in Brazil: (1) lack of susceptibility of

Brazilians, (2) meager density of pollen grains in the atmosphere, (3) shortness of pollination periods, and (4) weak allergenic capacity of the pollen. The authors, however, reached no conclusion on this interesting subject. According to their observations, among Brazilians the percentage of cutaneous sensitivity to pollen was very low. They reported on the principal anemophilous plants of Brazil.

Giscafre[47] wrote that the ornamental *L. lucidum,* that is cultivated commonly in the streets of the city of Santa Fe, was as serious a cause of hay fever as ragweed and grasses, in spite of its short pollen period.

Alvarez,[3] discussing pollinosis in Havana, noted that the prevailing winds, the geographic situation, the torrential rains in the summer, and the drought in winter did not favor the wide distribution of pollens in the air. In Cuba, the main pollinosis-producing species of plants did not exist. *Ambrosia* was rare. Relatively significant amounts of pollen from only the following plants were found in aerobiological studies: *Cynodon dactylon* (Bermuda grass), *Parthenium hysterophorus* (feverfew), *Mangifera indica,* and *Phoenix dactylifera. Casuarina* (Australian Pine) pollen presented a certain seasonal type and was the most abundant, but no person with hypersensitivity to it could be found. Hypersensitivity to pollen was rare. In a clinical series of 653 patients with respiratory allergy, only 4.1 per cent were found to be sensitive to pollen. On the whole, Havana possessed an ideal climate for clinical improvement in pollinosis sufferers.

From Australia, Morton[78] presented a comprehensive approach to the problem of the botany of an area and its relation to clinical allergy of the upper respiratory tract. The botanical factors in the investigation of seasonal hay fever were recorded. He gave a short description of his area, as to topography and meteorology. The potential hay fever flora of his district were examined and he noted that the most common cause of seasonal allergy of the hay fever and asthma type was anemophilous pollen of weeds and grasses. Hypersensitivity of patients to pollen of weeds alone was unusual, but generally was associated with hypersensitivity to pollen of grasses. Tree pollens played only a minor rôle in seasonal hay fever. He observed that the onset, severity, and duration of the hay fever season were bound intimately to the prevailing meterological conditions and varied from year to year.

Woringer[116] observed that allergy to the castor oil plant *(Ricinus)* occurred in handlers and laboratory workers. Clinically, the condition resembled pollinosis. The skin and mucous membranes reacted vigorously to extracts. The allergenic principle was present in the leaves as well as in the seeds. An active specific antibody was demonstrated in the blood, and the allergen was different from toxin ricin that could be isolated chemically. Sensitization occurred from inhalation.

Many attempts have been made to control and eradicate weeds. Both local and national government agencies have instituted laws which made it mandatory for a person owning land on which weeds are growing to eradicate them before they can pollinate. Recently, a bill was introduced in Congress, awarding a fund to set up methods for such a program. Now there is greater hope for the success of such a program, by the use of the so-called chemical weed killers. The state of Michigan intends to institute such a program. Grigsby[48] described such a method. A stock solution of di-nitro-ortho-secondary-butyl phenol, containing 4 pounds of the ammonium salt in one gallon of Diesel oil in kerosene 50 to 100 ml per gallon, completely killed ragweed within six hours and pollen release was stopped. Water solutions of this material killed more slowly and, using the same dilution, killing was incomplete. Other chemicals were tested but were not as effective. These results indicated that it was possible to stop pollen production in ragweed with chemical sprays. In the concentration used, most of the materials in this series were more or less toxic to cultivated crops. Smith,[102,103] discussing similar pollen control, stated that an aqueous compound of 2, 4, di-chlorophenoxyacetic acid of 1,000 ppm prevented pollen

shed if used early in the flowering stage. Experiments with a fog machine indicated that it was more economical than a spray. In Queries and Minor Notes,[85] in a discussion on a de-pollinating program, it was stated that chemical destruction was possible, but that it depended on the particular situation. As an example, if a community was insulated on all sides by a wide strip of water or forested lands, or if weeds were well established, it was almost impossible because of the longevity and abundance of viable seeds in the soil. Annual riddance could be accomplished by uprooting the weeds. This problem could be solved; however, the effort would have to be national and on a continuous basis because pollen, due to its buoyancy, could be brought in from a great distance by high winds.

ATMOSPHERIC STUDIES

A research council to study pollen distribution throughout the nation is being set up by the American Academy of Allergy.[81] There will be three major divisions: aero-allergens, foods-drugs, and pharmaceuticals. The first subject to be studied will be airborne substances causing allergies. Subcommittees will deal with pollens, molds, dusts, and miscellaneous allergens. In co-operation with the U. S. Weather Bureau, they will prepare a daily pollen count map that will be offered to newspapers for publication.

Dr. W. C. Jacobs,[80] Weather Bureau Climatologist, reported that the agency is planning to set up a "storm-warning system for hay fever and asthma sufferers" by which it will forecast, twenty-four to forty-eight hours in advance, the arrival of an air mass laden with ragweed pollen in a given area. Southern Indiana is the region having the greatest ragweed pollen density. Air currents carry pollen hundreds, and even thousands, of miles and the climatologists plan to follow these concentrations and map their courses.

Durham,[25,26] continuing his studies on atmospheric allergens, observed that there was a definite variation in the velocity of the fall of pollen grains in a 4-foot column of air. Some of this doubtlessly was due to the difference in the size of the pollen grains. Another factor might be the static changes imparted to the individual granules in their expulsion from the atomizer. As a result of this study, it was evident that some pollens, such as blue grass, Russian thistle, and oak, fell twice as fast as that of common ragweed. A final gravity count of these pollens should be discounted 50 per cent in order to have an approximately correct determination of the number of pollen grains in a given volume of air as compared to common ragweed.

As a result of five seasons of experimentation with various gravity-sampling devices controlled by parallel volumetric tests, Durham[25] stated that air samples should be taken on the unobstructed top of a tall downtown building. He described a sampling device which consisted essentially of two parallel planes of polished stainless steel, with the slide holder raised one inch above the lower plane. He submitted a conversion factor with volumetric conversion of pollen and fungus spore counts, presenting definite factors for about forty pollen and one fungus spore. Two sets of conversion factors were listed, so that counting might be done on the basis of one square centimeter of slide area, or on 3.6 square centimeters.

The National Pollen Survey Committee of the American Academy of Allergy[4] reported acceptance of a sampling apparatus devised by O. C. Durham, and also suggestions for standardization of the common procedures used in pollen counting.

CHEMISTRY OF POLLEN

Wodehouse and Coca,[115] in their review of the chemistry of pollen antigens, presented the following conclusions: (1) The molecular size of the antigen was large enough to make it nondialyzable through the usual semipermeable membranes, yet small enough to deny a protein character and to indicate that it was a complex

polypeptide. (2) It was resistant to heat and not heat-coagulable. (3) It gave a positive reaction to the biuret test. (4) It was not easily digestible. (5) It was a relatively weak antigen in lower animals, and it appears to be quite identical throughout the grass family. It appeared to be a common antigen in the tall and short ragweed and probably in all the other members of the ragweed family. In all the species of the chenopod-amaranth group which have been studied, there has been found a common antigen. Among the trees, the antigen appeared to have only a generic character, extending sometimes through related genera, and even whole families.

That much confusion still existed in 1946 was evident in the work of Sherman and Stull,[100] H. S. Baldwin et al.,[11] and K. Robbins, M. Mosko and A. Samuels,[79,91] although, in general, many investigators agreed on the chemical characteristics of pollen. The fraction S of Baldwin et al., which was the fourth alcoholic fraction, was negative to both the biuret and ninhydrin test and contained 1.4 per cent nitrogen. The fraction A of Robbins et al. was somewhat similar to fraction I of Cooke and fraction S of Baldwin.

Fraction A of Robbins et al.[79,91] is a heat stable fraction of water extract at pH 4.0 adsorbed on aluminum hydroxide, released by phosphate buffer at pH 7.4, and precipitated by alcohol. They concluded that their substance contained protein and thirteen amino acids were noted. In it there was a carbohydrate polysaccharide, containing hexose, pentose, and hexuronic acid, no hexamine, and 50 per cent protein and 50 per cent carbohydrate. This substance contained a very small amount of flavonal, demonstrated by spectrophotometric analysis, and was a more reactive agent than a whole ragweed solution of the same nitrogen content and total solids in ragweed-sensitive patients. Therefore, it was obvious that this substance, which they claimed was the skin reactive principle, appeared to be a complex protein carbohydrate.

STANDARDIZATION

Many attempts have been made to standardize pollen; however, there has been little unanimity as to the active principle, or principles. Each method tried eventually has been found to be faulty. Methods, using as a basis weight volume, total nitrogen, and protein nitrogen, have not stood the test of time. This probably was due to the fact that pollen contains more than one antigen. First, a standard method for the preparation must be accepted, then an evaluation of the various antigens can be undertaken. It has been agreed that one method will not solve this problem, but that biologic assay also will have to be done. Elmer Becker[12] reported a method of assaying ragweed pollen by means of the "Quantal" response. This assay was based on one biological property of ragweed pollen extract—the direct skin reactivity. This method of assay was an adaptation of the method of Bliss and consisted of using a number of different dilutions of a given extract and making skin tests on patients specifically sensitive to ragweed. The percentage of positive reactions to each dilution was transformed into probits and the probits plotted against the log of the dose (reciprocal of the dilution). A straight line resulted. The problem of assaying different solutions became the problem of comparing the dose-response curve. This method gave not only the estimate of the ratio of the potencies of two solutions, but an estimate of the error. This method has been validated for scratch test, and its validity for intradermal testing now is being investigated.

George E. Rockwell,[93] chairman of the Standardization Committee of the American College of Allergy, has reported a method of standardization which is a combination of a chemical and biological test. This method has been reported in a recent edition of the ANNALS OF ALLERGY. It is by far the most accurate method of standardization of allergenic extracts so far presented.

PROGRESS IN ALLERGY

IMMUNITY

Rackemann,[89] Alexander et al,[1] and Cooke did not believe that the concentration of thermostabile antibody always was proportional to the degree of clinical relief from symptoms of hay fever, that was the original concept of Loveless, but has not been corroborated. This may be due to the fact that the chemical structure of pollen has not been established.

A direct test for blocking antibody in patients treated for hay fever was reported by K. Maunsell[73] of England. This test detected and titrated the blocking antibody of Cooke, in the patient's skin. The development of a blocking antibody in the serum of subjects specifically treated for hay fever was confirmed by this method. The blocking titer was used as a guide in assaying chemical protection. No blocking antibodies were detected in subjects with hay fever treated with injections of nonspecific human isoserum. Instead of injecting a mixture of isoserum and pollen into nonsensitive skin, the skin of subjects with hay fever was tested with mixtures of their own serum and pollen. Thus, a "direct" blocking test with autoserum was developed.

Alexander, Johnson, and Alexander,[1] reported further studies in measurement of circulating antibodies and antigen. They noted that relief of ragweed hay fever usually was associated with elevated titers of thermostable antibody. However, the titers of thermostable antibody were not directly related to the amount of specific treatment, as there was marked individual variation. During the pollen season, circulating antigen was observed in treated and untreated patients, as well as in normal persons, and it was related to the pollen concentration in the air. From their work, it appeared that the circulating antigen did not cause symptoms and need not be considered in the treatment of hay fever. The values of circulating antigen and thermostable antibody did not correlate with reagin titer. In their experience, perennial treatment gave better results than preseasonal injections.

Mosko and Robbins[79] reported on the immunologic properties of their fraction, which supposedly was specific for the skin reaction in hay fever. The fraction could be injected into patients without producing significant constitutional reaction. It did not shock guinea pigs sensitized to whole ragweed, nor did it sensitize guinea pigs. Combined with gelatin or human gamma globulin, it became more able to produce systemic reaction in patients with natural sensitivity to ragweed, but did not produce shock in guinea pigs sensitive to whole ragweed. The authors thought that treatment with this fraction during the past ragweed season gave evidence of improved therapeutic effectiveness, warranting further studies.

Kulka and Hirsch[64] reported on a study of sensitization to ragweed extract and the production of antibodies by means of adjuvants. In rabbits under observation for two years, they noted variation of the antibody levels following repeated injection of ragweed extract and adjuvants, and the nature of antibodies passively transferred from the guinea pig sensitized to ragweed pollen extract. The rabbits were injected with ragweed pollen extract in water and in oil emulsions containing killed tubercle bacilli, and were observed over a period of two years. Repeated injections produced more vigorous sensitization and antibody formation than did a single injection. Once a maximum serum antibody level was reached, it could not be increased by further injection. In guinea pigs, injected with ragweed pollen extract with adjuvants, there developed antibodies capable of passively sensitizing normal human skin. These antibodies quantitatively were unrelated to colloid agglutinating titer. There was no relation between them and degree of skin sensitivity, or susceptibility to shock. The use of such substances might be of some value in clinical therapy, because of high antibody titer, for control of clinical symptoms.

Samter and Becker,[97] studying nasal secretions for the presence of specific reagins in ragweed-sensitive patients, noted that the nasal secretions of seven of ten patients were positive. Nasal secretions from normal persons were negative. They believed

that these observations might be significant for a better understanding of the clinical course of pollinosis.

Walzer and Golan,[114] reported on a series of experiments, demonstrating that antigen was transported through the body from the positive to the negative pole. It could be introduced into the body at either pole, but was transported only from the positive to the negative pole. It could be transported through more than one person in a relatively short period of time.

DIAGNOSIS AND SYMPTOMOLOGY

Brown et al[19] reported on a significant study of dyspnea and diminished vital capacity as a symptom and a sign in hay fever. They observed that of thirty-eight pollen-sensitive patients subjected to repeated vital capacity determinations all but twelve showed a diminished vital capacity during the pollen season. Some had asthma as a complication of their hay fever, but were free of asthma at the time the vital capacity measurements were made. They discussed the possibility that diminished vital capacity might represent latent bronchial asthma. In 30 per cent of the patients, the vital capacity was noted to undergo periods of reduction in the absence of any nasal or chest symptoms. In thirty patients, upper respiratory infections were associated with a significant drop in vital capacity.

London[71] reported on an interesting incidence of hay fever in an infant four months of age. Scratch tests were positive to short and giant ragweed and cockleburr. The patient responded to therapy and there has been no recurrence of symptoms since 1942.

Rosen[94] reported on a patient with hay fever followed by asthma, which occurred after maximum exposure to ragweed pollen. This patient was a soldier who previously had lived in an area where there was a much lower count. Prior to that time, he had not had any symptoms and there was no past personal or familial history. During the season, his reactions to skin tests were very large; after the season, they were small.

While in the army, the same author[95] observed 100 men, hospitalized because of asthma, with special reference to nasal and paranasal symptoms and findings. He found that fifty-five had perennial or seasonal nasal symptoms; of ten with seasonal hay fever and asthma, eight had hay fever prior to asthma and the other two had a simultaneous onset. Of fifteen patients with perennial asthma and seasonal hay fever, nine had the onset of asthma and hay fever simultaneously. In two patients, asthma preceded the hay fever, and in four, hay fever antedated the asthma. Examination of the nasal mucosa, by an ear, nose, and throat consultant, revealed positive allergic findings in eight of forty-five patients without nasal symptoms. Transillumination of the sinuses was positive in fourteen of forty-five patients without nasal symptoms and in twenty-three of fifty-five with nasal symptoms. X-rays of the sinuses were positive in twenty-seven of forty-five without nasal symptoms and in twenty-three of fifty-five with symptoms. Intracutaneous tests were positive more frequently in patients with nasal symptoms, especially to the pollens.

Jamieson[59] reported on a patient with asthma due to bee scent who also developed symptoms of hay fever. In *Clinics,* Leo H. Criep,[21] writing on allergic rhinitis, noted that in many patients with nasal allergy there developed obstruction of the eustachian tubes, with labryinthine vertigo as a secondary manifestation.

TREATMENT

Specific treatment for hay fever has withstood the test of time. Each year new methods for specific treatment are introduced, but none have been an improvement over the hypodermic method. The use of oral pollen and specific propeptanes of pollen have been given little encouragement in the literature.

Herrmann[55] discussed the inunction of allergens with "Intraderm." Sufficient clinical improvement in patients with allergy warrants its further study and observation.

Hansel,[51] using very small doses for treatment, reported excellent results. In hay fever patients, Hansel advocated the use of coseasonal therapy with small doses of pollen given intracutaneously. When possible, coseasonal therapy should be preceded by preseasonal treatment. The initial dose was determined by the dilution of extract which caused a 15 mm. wheal following intracutaneous injection. If this size wheal was produced by a 1:100,000 dilution, treatment was started with a .02 ml dose. The amount was increased by .01 ml every two to five days until the optimal dose was reached. In patients with moderate sensitivity it could be .05 ml of a 1:10,000 dilution. Small doses were used subcutaneously, preseasonally. He concluded that small doses of pollen give satisfactory results in the majority of patients.

Rackemann,[87,88] discussing future problems in allergy, stated there were two parts to the treatment of pollinosis: (1) Specificity of the treatment and selection of proper pollen and (2) mechanics and technique of treatment. He was not sure that treatment with a mixture of various pollen extracts was correct. According to him, skin tests, in themselves, were not an accurate criterion of the pollens to which the patient was sensitive. He stated there were too many false positive reactions and too many patients who were clinically sensitive yet showed no skin reaction. The skin test was a test of the skin and might or might not reflect the sensitiveness of the nasal or bronchial mucosa. The point he made was that the clinical history was, after all, the best index of the substances to which the patient was sensitive. He pointed out that some of the so-called late ragweed sensitivity could be mold sensitivity. He stated that specific mold sensitivity was very striking and that, in pollen surveys, local conditions were very important, such as peculiar air currents and backyards. In treatment, much of the difficulty, such as reaction, might be overcome if ragweed antigen could be separated into a skin-sensitizing fraction and an immunizing fraction. So far, no satisfactory method has been developed to accomplish this separation.

ANTIHISTAMINE DRUGS

Probably the outstanding feature in this year's literature has been the plethora of papers on the use of the antihistamine drugs, benadryl and pyribenzamine. However, it is interesting to note at this point that Loew, Macmillan, and Kaiser[69] reported that, from some experiments on guinea pig serum using benadryl to antagonize histamine and barium and acetycholine, they noted that benadryl could not be regarded as a specific histamine antagonist.

Benadryl is one of the histamine-neutralizing substances which has received a great deal of publicity and on which some very encouraging clinical reports have been presented.

Logan,[70] reporting on the use of benadryl in allergic diseases of children, stated that his results indicated that the drug was useful if employed in an adequate dosage.

Code,[20] in the Proceedings of the Staff Meetings of the Mayo Clinic, gave a comprehensive review on benadryl as an antihistamine substance, on the antihistamine substances which led to its development, and on its mode of action in anaphylaxis and in allergy. He discussed its mode of action in drying the secretions associated with hay fever and in producing dryness of the mouth. A very excellent bibliography accompanied this report.

Jenkins, Schrieber, and Sheldon[60] reported on the use of benadryl in the treatment of hay fever and asthma. From this, it appeared that it was a valuable adjunct in the control of certain of the hay fever symptoms of grass and ragweed pollen-sensitive patients. Those symptoms were rhinnorrhea, itching of the nose,

sneezing, itching and watering of the eyes, and itching of the throat and palate. Nasal obstruction and fatigue which accompany pollinosis frequently are not relieved by this drug. In patients with bronchial asthma due to grass and ragweed pollen, there was significant subjective improvement in only six (26 per cent) of twenty-three patients. Unpleasant reactions to benadryl occurred in 75 per cent of all patients studied. Waldbott,[113] commenting on his clinical results with benadryl, noted that it was of great value in treating infants with asthma. In his series, he had what he classified as complete results in 32 per cent of patients with asthma, 51 per cent complete results in those with hay fever, 43 per cent complete results in the ones with vasomotor rhinitis, and 80 per cent complete results in patients with urticaria. He felt that the action of this drug was most impressive, although by no means ideal because of unpleasant side effects in a large number of patients. He raised the question as to whether or not there might be a spontaneous sensitivity to this drug, due to the fact that three patients suffered asthmatic attacks shortly after ingesting it. His findings would indicate that the drug was more effective on the allergic wheal than on bronchospasm.

Levin,[66] treated seventy-eight hay fever patients with benadryl, some of whom were receiving hyposensitization therapy, although some were not. Fifty-nine per cent of the ones receiving the drug reported good symptomatic relief. Side reactions were less frequent in children. A number of patients were relieved by the drug on certain days and not on others, even though larger doses were taken. (It would have been interesting to have had data as to the pollen counts and opportunities for exposure on those days.) He did not observe any patient with hay fever whose symptoms had been aggravated by benadryl. In some patients, who were given the drug in 100 mg. doses twenty minutes prior to scratch testing, no appreciable influence upon the skin tests was noted.

Of fifty-two patients with hay fever treated with benadryl by Koelsche, Prickman, and Carryer,[61,62] thirty-nine were benefited. Of nineteen with both asthma and hay fever, fourteen patients benefited. In twelve patients with bronchial asthma alone, only four were relieved.

Zolov,[117] commenting on the use of benadryl, stated that it was a powerful new chemical compound which possessed antiallergic activity and beneficial effects might be expected within a few hours after its administration. He observed that the most frequent side effect was dryness of the mouth. However, not infrequently, transitory drowsiness might be alarming. The use of the drug for asthma had not been very encouraging, and he believed that its most successful therapeutic application would be for patients with hay fever, urticaria, and vasomotor rhinitis. Thacker,[110] reporting on its use in seventy-two patients with vasomotor rhinitis, perennial allergic rhinitis, and nasal allergy associated with asthma, noted that complete relief was obtained in 50 per cent of the first, 42.8 per cent of the second, and in 50 per cent of the third group. He concluded, however, that benadryl certainly was not the solution of the allergic problems which face the physician and his patients.

Schwartz and Levin[99] used this preparation in fifty patients with various allergic manifestations and observed that symptomatic relief was obtained in eight of twenty patients with asthma, in six of ten patients with vasomotor rhinitis, in four of five patients with chronic urticaria, in all of eight patients with acute urticaria, and in three of seven patients with miscellaneous allergies. The majority of their patients reported benefit within one hour after administration; symptomatic relief was palliative and side reactions occurred in thirty patients. The side reactions in twenty-six of these patients disappeared gradually, even though administration was continued. The other four stopped the drug, due to the severity of their symptoms.

Eyermann[37] used benadryl in fifty-two patients with pollinotic vasomotor rhinitis and completely relieved the symptoms in 67 per cent. In 23 per cent of this group,

the sneezing was relieved, but not the other associated symptoms. In 9 per cent of these patients, no symptoms were relieved. In all patients relieved, the symptoms recurred promptly when the drug was stopped. He stated that the palliative effect in a high percentage of patients with pollinotic vasomotor rhinitis and urticaria would support the hypothesis that histamine or a histamine-like substance was released during an allergic reaction. However, the relief of the symptoms was not conclusive proof that they were due to histamine. The instances in which the itching and sneezing were controlled, but the turgescence of the turbinates was uninfluenced, and the instances of this ineffectiveness in wheezing and dyspnea, suggested that factors other than histamine were responsible for the total clinical picture.

Bowen[16] concluded that benadryl had a true place in allergy and obtained its best effect in patients with chronic urticaria. He also believed it was an excellent aid for patients with allergy due to ragweed and noted improvement in 60 to 70 per cent of such patients. One of five patients had sleepiness as a side effect; however, this was minimized by the administration of caffeine or benzedrine. He felt that benadryl should be used carefully in any aspirin-reactive patient. He stated that the use of benadryl did not exclude thorough allergic investigation and that its place is only as an adjunct in the management of allergic patients. His paper included some unpublished figures which we quote here: Parke, Davis & Co. investigators[83] reported on 404 patients with 82.4 per cent improvement. Derbes reported 70 per cent improvement and Efron, 65 per cent. In patients with the so-called "hay fever x," so frequently encountered in the South, benadryl helped 30 per cent. In contradistinction to such glowing reports, Friedlaender[42] noted no apparent benefit from its use in hay fever and stated that his results suggested that histamine might be a more important factor in urticaria than in other allergic conditions.

In 188 patients, Todd[111] was impressed with the rapidity of action of benadryl and with the full therapeutic effect of relatively small doses on acute manifestations; for chronic conditions more was required. Eleven of his patients suffered from seasonal rhinitis due to pollen and complete relief was obtained in all of them. The chief side effects were: drowsiness, dizziness, dry mouth, and nervousness. They occurred in a considerable percentage of patients using the drug; however, the duration usually was very brief. He cautioned that, although no acquired allergy to the drug had been reported, this possibility must be kept in mind.

Harley[52] treated five patients who were grass pollen-sensitive; three of them obtained prompt and complete relief; one was greatly improved; but the fifth received no benefit.

Stroh[108] recommended benadryl as a palliative treatment until allergic investigation could be made. He believed that its side reactions were far too frequent and unpredictable. Its use was beneficial in controlling itching and also for its sedative action. It was of value for treating hay fever, but failed for acutely aggravated allergic manifestations.

An interesting sidelight on its side effects was reported by Davison,[24] in a letter to the International Correspondence Society of Allergists, in which he noted that benadryl caused the fetal movements to stop after its ingestion by a pregnant woman. The mother became sleepy and apparently her baby went to sleep too. When the drug was stopped, the movements of the child began again and there were no untoward effects.

An anonymous contribution[8] on the subject of benadryl appeared in the *American Professional Pharmacists,* in which it was stated that benadryl seemed to be a potent antihistamine agent, although the mechanism of its action was not understood fully. Its action in drying the secretions accompanying hay fever and in producing dryness of the mouth might be due to blocking of the secretagogue action of histamine. The shrinking of the mucous membrane and the disappearance of wheals might be due to its antihistamine effect on blood vessels.

Friedlaender and Feinberg[44] reported that the local application of benadryl exerted a marked reduction in the whealing reaction in ragweed-sensitive subjects. This would suggest that histamine, or a histamine-like substance, plays a role in the promotion of the wheals. They stated that the action of the drug was thought to be produced by displacement of histamine from its site of action. It was suggested that its failure when administered orally to affect materially certain types of allergy, in which histamine was thought to play a role, might be the result of insufficient drug reaching the site of action.

It might be well at this point to note that, in the October, 1946, issue of Parke, Davis and Company's[83] *Therapeutic Notes*, there was a summary on the histamine concept of allergy, and a review of the literature on benadryl, its pharmacology, clinical use, dosage, and side reactions.

Another histamine antagonist which, from published and many unpublished reports, has appeared to be even more effective than benadryl, both from the therapeutic standpoint and because of a lower incidence of side effects, is pyribenzamine.

In his article, Epstein[36] presented the conclusion that pyribenzamine and benadryl were very efficacious in the symptomatic treatment of patients with urticaria and hay fever and, to a lesser extent, those with perennial rhinitis, asthma, atopic dermatitis, and other forms of allergy. He believed that there was not much difference between the two drugs in their clinical efficacy, and quoted the following percentages of relief obtained—95 per cent in patients with acute urticaria, 80 per cent in those with chronic urticaria, 80 per cent in patients with hay fever and extrinsic allergic rhinitis, and about 40 to 50 per cent in those with bronchial asthma. He further stated that their usefulness is limited, since they exert only a symptomatic effect. However, as he pointed out, such relief might equal a clinical cure in self-limited allergies, such as attacks of acute urticaria, drug eruptions, or hay fever. He noted that they were of low toxicity when given orally and were tolerated well. He cautioned, however, that the natural limitation of these drugs should be kept in mind and that we should not be overoptimistic.

Feinberg,[39] writing on histamine antagonists, summarized his presentation by stating that, even at that early stage of experimentation, it was evident that the use of benadryl and pyribenzamine would be limited because they would not be effective in many of the manifestations of allergy and because of toxicity and undesirable reactions. Further limitation was of course evident from the fact that, at best, such remedies were only palliative and did not produce any lasting benefit.

In an editorial[29] in the ANNALS OF ALLERGY, there was presented a brief critique of the newer antihistamine drugs, as well as some pertinent statements on histamine. It was stated that, although these antihistamine drugs undoubtedly relieved a certain percentage of hay fever patients, they did not offer any cure or hope of cure when used alone. It was interesting to note at that point that hay fever patients with mild symptoms also were often relieved by sedatives, hot drinks, or rest. Seven patients with hay fever benefited very little from antihistamine drugs. Large doses were apt to cause side reactions in many instances. In the editorial it was stated further that if wheal formation took place on cutaneous testing, a good response to benadryl or pyribenzamine might occur, but erythematous reaction to skin tests usually pointed to failure when these drugs were employed. Most patients with mild and moderate hay fever responded to specific immunization procedures, but in patients with more severe allergy there was a fairly large number of failures. The antihistamine drugs did not fill this gap. One ray of hope could be offered—a combination of these two forms of therapy. In many patients, who were very sensitive to ragweed pollen and were unable to receive a sufficiently high dose of pollen extract without reaction, the reaction could be controlled with benadryl or pyribenzamine. The author of the editorial believed, however, that it was too soon to make a proper evaluation of these drugs.

There were further comments in this same journal on the subject of benadryl,[33] that the clinical evaluation of this drug as an antihistamine compound was open to serious question. No doubt it had a useful place in medicine as an adjuvant measure, but where this usefulness would be had to be determined. In the editorial was brought out the fact that there was a strong sedative reaction with this drug, which should be viewed as a primary rather than a side reaction, and that adequate control studies, using narcotics, sedatives, or hypnotics which produce drowsiness in approximately 50 per cent of the patients, should be used for comparison of their effect on patients with asthma, hay fever, and urticaria.

An editorial[35] worthy of note appeared in *Medical Times* in which were reviewed some pertinent facts on histamine and its possible relation to allergy. There was a summary of the use of benadryl as an antihistaminic, its toxic reactions, and possible mechanism of action and the conclusion was presented that the results reported on this drug left little doubt that it, or some other like it, would have a definite place in therapy.

Feinberg[38] presented a masterful review of histamine and antihistamine agents, in which he stated that benadryl and pyribenzamine were useful symptomatic remedies in the treatment of seasonal hay fever. He felt that their order of effectiveness was pyribenzamine, neoantergan, and benadryl. Both pyribenzamine and benadryl caused a high incidence of side reactions, among which sedation and drowsiness were most common; these reactions were more frequent and of greater intensity with benadryl. In the use of these agents, the following should be considered: (1) A cure or lasting improvement was not to be anticipated. (2) At best, they exerted a temporary palliative action. (3) Many patients would fail to respond to them. Specific allergic methods should not be abandoned, as at that time they were the sole means of achieving lasting results. Another fact to be kept in mind was that the remote toxicity, in contradistinction to the immediate reaction, had not been studied sufficiently up to that time. To the best of his knowledge, these drugs acted by competing with the liberated histamine in their attachment to the receptor cell. Therefore, the benefit was only symptomatic and lasted for only a few hours after each dose. It was important to keep in mind the possibility that, while the patient was being helped temporarily by one or the other of these drugs, the long term program of creating immunity might be interrupted by this same drug if it was noted that they interfered with desensitization.

In *The Journal of Allergy*, in an editorial[34] on the subject of histamine antagonists, it was stated that patients in the acute sneezing and coryza stages of hay fever were influenced favorably by benadryl and pyribenzamine, but those with the congestive nasal obstruction of the later stages of hay fever or perennial vasomotor rhinitis were relieved to a much lesser extent. In patients with these types of allergy, pyribenzamine produced a more favorable response. The pollen-sensitive patients with asthma, who neglect their desensitization program because of their reliance on these drugs, will be disappointed greatly. The side effects of these drugs were becoming increasingly evident. Benadryl produced a marked soporific effect in a high percentage of patients. Disregard for this particular action and the resulting lack of alertness in the person might lead to accidents. Pyribenzamine had a similar action, but to a much lesser degree and less frequently. It had, however, other toxic actions. One of the most frequent was an excitatory effect consisting of nervousness, tremor, tachycardia, weakness, and insomnia. Not infrequently, a combination of sedation and stimulation was observed. At times, inability to concentrate and mild mental confusion occurred. Anorexia and gastric discomfort also might develop. Benadryl might also produce any of these symptoms. At best, these remedies were only palliative, a fact which should be emphasized to the patient. Unless this was continually observed, great harm could be done by dis-

ruption of desensitization programs. Many types or phases of allergic phenomenon were not relieved by these compounds. A very important fact was pointed out, that more prolonged and more extensive observation might disclose more intense or delayed toxic action of these drugs. Extensive experimentation with these and new synthetic compounds was in progress, and this search might yield more basic remedies.

An editorial[32] appeared in the *Canadian Medical Association Journal* presenting a summary of the Mayo Clinic reports. From this it would appear that benadryl prevented at least some of the pharmacologic actions of histamine, and was particularly effective in allergic patients when the underyling problem was edema provoked by release of histamine or histamine-like substances. Dramatic relief of symptoms occurred in patients with urticaria. However, the results were much less striking in hay fever. The side effects reported with significant frequency were sleepiness, dizziness, dry mouth, and nervousness.

Mayer et al,[76] investigating the toxicity of pyribenzamine, reported that six human beings tolerated up to 500 mg. of this drug daily, given in 100 mg. tablets. Mild sedation in one and mild nausea with "pelvic heaviness" in another of these subjects were the only untoward symptoms. The toxicity and antihistamine action of pyribenzamine were such that extended investigations were warranted.

In another article, Mayer[75] gave a good discussion of some antihistamine substances, including their chemistry, antihistamine activity *in vitro* and *in vivo*, their effect on anaphylaxis in guinea pigs and in dogs, and some thoughts on their mechanism of action.

Arbesman, Koepf, and Miller,[10] reporting on some of the properties of pyribenzamine, noted that it had potent antianaphylactic activity demonstrated by passive anaphylactic experiments in guinea pigs. When administered orally to human beings, there was a decrease in the size of histamine skin wheals in eighteen of twenty-eight patients. The skin reactivity of fourteen of twenty-four allergic patients diminished following oral administration of this drug. In September, the Committee on Pharmaceuticals and Medicaments of the American Academy of Allergy,[6] stated that it seems obvious that pyribenzamine was a useful palliative drug for certain allergic diseases, such as acute vasomotor rhinitis, seasonal and nonseasonal, and acute urticaria. It appeared to be less effective for the relief of asthma and dermatitis. They stated further that it would take a longer time to make a final evaluation of this drug, but it seemed safe to say that at that time it was very useful for symptomatic control. There was some indication that tolerance might be established if it was used over a long period of time; it was not a cure for allergic diseases.

Arbesman, Koepf, and Lenzer[9] made clinical studies with this drug on 495 patients. It relieved sneezing, rhinorrhea, and nasal occlusion in 75 per cent of 313 patients with allergic rhinitis. Results were better in patients with seasonal pollinosis than in patients with the perennial, so-called extrinsic or intrinsic type. They noted that it was apparently harmless in effective doses, but had some undesirable, although not serious, side effects. In eight patients, 100 mg. of pyribenzamine, one half hour prior to treatment, was capable of preventing constitutional reactions which ordinarily would occur with that dose.

Koepf, Arbesman, and Munafo, [63] studying the effects of chronic toxicity of the drug, observed no effect on the general behavior of dogs to whom they had administered 50 to 100 mg. daily for a prolonged period (one year). Hematopoiesis was not altered in these animals, nor did the drug produce a febrile reaction or impair liver or kidney function. In three human beings who were given 150 mg. of pyribenzamine daily for eighty days, no chronic toxic changes were noted. They noted, however, that such limited studies on human beings were not sufficient to warrant considering the drug completely harmless.

Friedlaender and Friedlaender[45] used pyribenzamine for various types of allergic disorders and noted that it afforded symptomatic relief in many patients with seasonal hay fever, perennial allergic rhinitis, and urticaria. Its action on asthma was negligible. Side effects, consisting of drowsiness, gastrointestinal upsets, and vertigo, occurred in 27.2 per cent of their patients. They felt that it was a valuable symptomatic drug for use as an adjunct to specific therapy.

Our own experiences with benadryl and pyribenzamine would, in general, seem to be similar to the ones previously mentioned. We have noted that pyribenzamine has been more effective, both from a therapeutic standpoint and from the standpoint of less frequency of unpleasant side effects. It would be apt at this point to state, as Feinberg did, that it is hoped that the advent of this type of therapy will not cloud the issue, nor dampen the ardor of our search for information of more basic value, that will help us to understand the mechanism of the allergic reaction and the constitutional background of allergy and find means for the connection of both.

OTHER THERAPEUTIC AGENTS

A few articles on other therapeutic agents were published this year.

Meier and Bucher,[77] reporting on antistine, a new synthetic antihistamine substance, stated that its specific effect is its antagonism to histamine. In their experiments with animals they found that when applied locally as well as generally, it had an antihistamine action. They found that when it was applied locally in experimentally-produced conjunctivitis, it produced noticeable improvement. The preparation also proved effective in anaphylactic conditions. In another article they presented their observations on the influence of antistine on antibody production, and concluded that it did not inhibit the antibody production stimulated by repeated antigen injections. In fact, antibody production was increased in these animals; perhaps, as they suggested, because of the protection given by antistine allowing the animals to tolerate a much larger amount of antigen.

Bourquin[17] found that antistine was of great value, since it gave relief to many patients suffering from hay fever. Because of its low toxicity, he recommended it for all allergic conditions of the eye.

Schindler[98] used antistine in thirty-nine patients with allergic conditions, at the Medical Clinic of the University of Basel. Ten of these patients had bronchial asthma and eleven had urticaria, none apparently were hay fever patients. He found the therapeutic effect to have been very good for urticaria, and good for some patients with asthma. The average daily oral dose was 300 mg., but 600 mg. also has been tolerated. Subcutaneous and intravenous methods of administration also were used.

Feinstone, Williams, and Rubin[40] introduced a new antihistamine drug, hetramine, and its activity was demonstrated in laboratory animals. They felt that this drug might have a beneficial effect on some of the varied symptoms associated with hypersensitivity. Clinical trials are being conducted now in a variety of conditions including hay fever, urticaria, and physical allergy.

Loew, Kaiser, and Anderson[68] reported on the antihistamine action of five alkyloxytriazines in guinea pigs, and noted that they were two to ten times as effective as aminophyllin.

An article by Ghiselin,[46] on the use of anthallan, received some publicity in the East. His study was conducted on forty-two patients with seasonal and nonseasonal hyperesthetic rhinitis.

At the start of treatment, the patients had suffered from their disease for an average time of 506 days (from eleven days to five years). With the customary methods of treatment, they had had only short periods of relief. In forty out of

forty-four (90 per cent) courses of treatment with anthallan, a beneficial influence of the drug was observed. The improvement varied between 25 and 100 per cent subjectively and objectively, as evaluated by an arbitrary schedule of numerical ratings of all the subjective and objective manifestations involved. The persistence of improvement was observed for an average of fifty days (7 to 248 days). Laboratory studies and examinations did not indicate any harmful effect of treatment with anthallan. He concluded that anthallan in doses of three to twelve capsules daily was a useful drug for obtaining relief in a high percentage of patients with seasonal and nonseasonal hyperesthetic rhinitis and that it could be used with complete safety.

In an editorial[31] in the *Journal of the American Medical Association,* there were comments on this article, stating that it was difficult to appraise the effectiveness of anthallan from the treatment of forty-two patients who formed the clinical material of this report. In the editorial, it was stated further that the author attempted to evaluate results by a complicated system of assigning numerical values to the symptoms of the patients, averaging them and comparing them with similar averages derived from numerical values assigned at the end of treatment. Because of such statistical manipulations, scientific appraisal of the effects of this drug based on this report was difficult. Also, the study did not include controls, so more scientifically controlled investigations certainly were indicated.

An article on the use of hapamine appeared, in which Eden[28] reported successful treatment of seventeen children with allergic rhinitis, with this preparation. Except in one instance from which one might deduct that the patient was sensitive to spring and fall pollen in addition to other substances, the details of the sensitivities of the patients were not given.

A report of the Committee of Pharmaceuticals and Medicaments of the American Academy of Allergy,[5] presented this year, recommended the removal of torantil and hapamine advertisements from *The Journal of Allergy.*

Following local anaesthesia, Dimow[23] injected a 10 per cent solution of calcium glucono-glacto-gluconate into the submucosa at the base of both inferior nasal turbinates of patients with allergic rhinitis. Hardening of the turbinates occurred with sclerosis. Sneezing, rhinorrhea, and itching were relieved in some patients after the first injection, and development of polypi was prevented. About 90 per cent improvement was obtained.

An article on ethylene disulphonate appeared, in which Blumenthal[14] reported on treating eighteen patients with three injections a week, twelve of whom had asthma and six had allergic rhinitis. The results were negative.

It is interesting to include here the report of the Council on Pharmacy and Chemistry[7] which presented the conclusion that, from a review of the published reports, the statement of the AMA chemical laboratory, and the reports received from physicians investigating the use of ethylene disulphonate in the treatment of various allergic conditions, not only was it evident that the existence of such a compound was open to serious doubt, but that the theory of its dilution and supposed part as an oxidation catalyst of carbohydrate metabolism was based on flimsy biochemical conjectures that had no proven connection with the mechanism of allergy, if indeed there was any. Examination of the product indicated that, by ordinary tests, it cannot be distinguished from distilled water, and the council declared it was not acceptable for inclusion in N.N.R.

MISCELLANEOUS

Gutmann[49] stressed the importance of history taking in patients with allergic disease, stated that it often led to an explanation even without tests, and cited a number of instances by giving case histories.

Squier[106] also stressed the importance of a complete history, stating that such a

history provided data of inestimable value in etiologic diagnosis. He noted that clinical sensitivity might be present in spite of negative skin tests. The converse also was true. Skin test information must be correlated with the history and clinical observations. In specific management, avoidance of contact with causal agents and specific hyposensitization were the two fundamental principles. Squier and Rackemann pointed out that, in hyposensitization, caution must be exercised against exceeding the threshold of attained tolerance; overtreatment must be avoided.

Stiles and Johnston,[107] in a study of the inheritance of respiratory allergies, traced a family for five generations and 232 people. The incidence of allergies was 23.4 per cent as compared to 7 per cent in the general population. The specific sensitivity did not appear to be inherited, but rather the capacity, or predisposition, to become hypersensitive. From their data they suggested that respiratory allergy might be interpreted as an irregular dominant characteristic.

Rittwagen, Romano, and Svigals,[90] studying 100 children with rheumatic fever, noted a definitely higher incidence of allergy in the rheumatic patients and in their families. The most frequent allergy was seasonal hay fever.

Hulett[56] reported a screening test for the identification of allergic states that he felt was safe and reliable. He used histamine hydrochloride and injected 1/20 c.c. of 1:100,000, 1:10,000, and 1:1,000 dilutions.

Mausmann[74] felt that the eosinophilic response was used very little; and yet contained much information. Every patient with a nasal secretion, whether acute or chronic, should have a nasal smear.

Dutton,[27] in discussing nasal and sputum smears, stated that the failure to use this valuable procedure was perhaps technical or because of attempting to draw conclusions from inadequately obtained material or too few observations. He stated that the test must be repeated before conclusive evidence could be drawn.

Samter[96] made some interesting experimental studies on eosinophils. Normal saline, histamine in various concentrations, and specific antigen were introduced by spray into the nasal cavity of 198 unselected patients with pollinosis, prior to and during the season. Secretory response (amount and consistency), eosinophilic response, and peripheral eosinophil count were recorded.

1. No parallelism was found to exist between secretory and eosinophilic response.

2. The secretory response, though distinctly exaggerated in most patients with latent nasal allergy, was nonspecific; the eosinophilic response was specific, but only a fraction of the patients responded to introduction of specific antigen, prior to the season, with nasal eosinophilia.

3. Evidence was presented, however, that histamine might be an important exception to this rule; significant differences were noted in the eosinophilic response of patients to histamine administration, prior to and during the ragweed season.

4. Neither secretory nor eosinophilic response obtained prior to the season permitted any prediction of the clinical course.

Hayden[54] reported chromidrosis occuring in a patient with ragweed pollinosis, which developed while she was receiving ragweed hyposensitization and recurred each year for several years.

Parsons[84] reported the use of the sedimentation rate as a diagnostic aid in allergy. In all his hay fever patients, the sedimentation rate was normal. He concluded that many patients with hypersensitivity had complicating diseases which are not of an allergic nature.

Troescher, Ancona, and Kerr[112] found a histamine-like substance present in nasal secretions of the common cold and allergic rhinitis. A method for extraction of this substance was described. There was no striking difference in total histamine activity in the two conditions. There was no apparent correlation between the number of eosinophiles and amount of histamine present in the nasal secretion.

PROGRESS IN ALLERGY

NEW BOOKS AND REVIEWS

A number of excellent books have been published this year, in which pollinosis is discussed.

Feinberg's[121] second edition, "Allergy in Practice," is a very comprehensive textbook. This edition contains a chapter on histamine in anaphylaxis and allergy by Carl Dragstedt and a chapter on histamine antagonists.

Urbach and Gottlieb's[125] second edition of "Allergy" is probably the most complete reference book on allergy ever published.

The new text by Robert Cooke[118] contains much to be digested and much original work on the subject of the chemistry and immunity of pollinosis. An excellent chapter on immunochemistry is presented.

Volume 5 of "The Clinics," "Therapy in Allergy"[122] is a comprehensive survey of the subject of pollinosis.

Gay's[123] "The Diagnosis and Treatment of Bronchial Asthma" contains the author's concept of the treatment of pollinosis.

Derbes and Englehardt's[120] "Treatment of Bronchial Asthma" contains many excellent chapters on pollinosis.

Two popular books have appeared this year which include a discussion of this subject: "What You Don't Know May Hurt You," by Rudolph and Rose,[124] and "It's an Allergy," by Frank G. Crandall, Jr.[119] This type of book gives much information to the sufferer, but also leads to many erroneous conclusions and well intended misinformation.

Among the excellent reviews appearing are those of Rackemann,[87,88] Hansel,[50] Macquiddy and King,[72] and Rockwell.[93]

A popular concept of hay fever, "Fact and Fiction," is discussed by Fleming.[41]

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The Use of Intravenous Ethyl Alcohol

(Continued from Page 195)

quent, complete report. The present preliminary notes, it is hoped, will stimulate further investigation by other workers in this field.

Subsequent to the writing of this paper, the treatment has been used on twenty-six patients with similar results. Dr. John D. Gillaspie of Boulder, Colorado, who accidentally discovered the same treatment, reported to the members of the Mississippi Valley Regional Postgraduate Course that he had noted the same effects when ethyl alcohol was given intravenously to five patients with severe bronchial asthma.

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News Items

LOS ANGELES SOCIETY OF ALLERGY

A new allergy organization has been formed in Los Angeles County, under the name of Los Angeles Society of Allergy, as a section of the Los Angeles County Medical Association.

The following officers were elected for the year 1947: President, Dr. George Piness, Los Angeles; vice president, Dr. Willard S. Small, Pasadena; secretary-treasurer, Dr. Frank G. Crandall, Jr., Los Angeles. There is a Council of four members who, with the officers, constitute an Executive Council.

Members of the Los Angeles Society of Allergy must be members, in good standing, of the Los Angeles County Medical Association. The organization is composed of active and associate members. The active members must be certified diplomates in one, or more, of the following: (a) The American Board of Internal Medicine—subspecialty allergy, (b) The American Board of Pediatrics—subspecialty allergy, or (c) The American Board for the Certification of Allergists—or a Fellow or Member of the American Academy of Allergy, or a Fellow or Member of the American College of Allergists. Associate members are physicians in Los Angeles County Medical Association, who are interested in allergy or practice allergy but, otherwise, do not fulfill the qualifications required for active membership.

It is planned to hold four regular meetings each year and any special meetings which may be required.

Under the auspices of the Los Angeles Society of Allergy, a committee composed of Drs. Piness, Small, Hyman Miller, and Lyle C. Bacon, has proposed a fee schedule for the diagnosis and treatment of allergy patients under the medical care program of the California Physicians' Service and the Veterans Administration. Leading allergists in other areas in California have been contacted, and it is planned to hold a conference at San Francisco in the near future with the executives of the California Physicians' Service and Veterans Administration to discuss and, if possible, secure approval of the fee schedule proposed for this state.

RESEARCH AWARD OF THE AMERICAN PHARMACEUTICAL MANUFACTURERS' ASSOCIATION

Dr. Bernardo Alberto Houssay, of Buenos Aires, was the recipient of the first annual Research Award of the American Pharmaceutical Manufacturers' Association. He received this award in person at Boca Raton, Florida, on April 28, at the fortieth annual meeting of the Association.

Doctor Houssay, who until recently was Professor of Physiology at the Medical School of the University of Buenos Aires, is an authority on the interrelationship of the various hormones. It was through his work that the relation of the pituitary gland to diabetes was firmly established.

In recognition of his work, Doctor Houssay also has received many honorary degrees, including medical degrees from Asuncion University in Paraguay, the Medical School of the Catholic University of Santiago, Chile, and the Medical School in Paris. The University of Toronto awarded him the 1945 "Charles Micle" prize for his work in medicine.

In this country, Harvard University conferred on Doctor Houssay an honorary degree of Doctor of Science. He was honored similarly by the Medical School of the University of São Paulo, Brazil.

Doctor Houssay is a former president of the Medical Academy at Buenos Aires

and is a member of many other medical academies, including those of Rio de Janeiro, Madrid, Mexico, and Lombardy, and of the Royal Society of Edinburgh. He is an honorary member of the American Academy of Arts and Sciences in Boston, the Physiological Society of Great Britain, and the American Physiological Society, and is a member of the Harvey Society of New York. He is an officer of the Order of Leopold and an officer of the Legion of Honor.

NORTHERN CALIFORNIA ALLERGY SOCIETY

On April 23, about twenty allergists from San Francisco and the East Bay region (Oakland) met and officially organized the Northern California Allergy Society.

The Nominating Committee selected the following officers: President, Dr. Albert Rowe, Oakland; vice president, Dr. Samuel Hurwitz, San Francisco; secretary-treasurer, Dr. Minnola Stallings, San Francisco.

Dr. Milton M. Hartman, San Francisco, was authorized to prepare a summary of recommendations and observations relative to the fee schedule for the diagnosis and treatment of allergy patients, which could be presented to the Veterans Administration and sickness insurance organizations. This summary also is being presented before the California State Medical Association convention in May.

CENTRAL PENNSYLVANIA ALLERGY SOCIETY

The Spring Session of the Forum of Allergy of the Central Pennsylvania Allergy Society was held in Reading, Pennsylvania, on Wednesday, March 26. The meeting was attended by a large and enthusiastic group.

Among the notable physicians who appeared on the program were Dr. Harold Abramson who spoke on "The Present Status of Allergy," Dr. Bela Schick who read a paper on "The Allergic Child and the General Practitioner," and Dr. Carroll Wright who presented "Treatment of Various Allergic Dermatoses."

Dr. Ralph M. Mulligan, secretary-treasurer of this Society, has compiled a booklet, *Thirty Questions and the Allergist,* which gives authoritative answers to questions asked by physicians, who do not specialize in allergy, and their patients.

SOUTHWEST ALLERGY FORUM

The meeting of the Southwest Allergy Forum was held on March 31 and April 1 at the Washington-Youree Hotel, Shreveport, Louisiana. Over 100 men from eighteen states attended.

The following officers were elected: President, Dr. Herbert Rinkel, Kansas City, Missouri; vice president, Dr. Sim Hulsey, Fort Worth, Texas; secretary, Dr. Fannie Lou Leney, Oklahoma City, Oklahoma. Dr. Carroll Pounders and Dr. Nesbitt Miller, both of Oklahoma City, were elected to the Board.

The 1948 session will be held in Oklahoma City at Easter time, and in 1949 the meeting will be in El Paso, Texas.

NAVAL AIR RESERVE TRAINING COMMAND

The following notice has been received from the Naval Air Reserve Training Command:

"The Naval Air Reserve Training Command, with headquarters at Naval Air Station, Glenview, Ill., has 17 nationally located Naval Air Stations and 4 Naval Air Reserve Training Units at which Naval Reserve Medical Officers may serve on active duty with full pay and allowances and with the privilege of returning to civilian life at any time upon request. Additional details may be obtained from Chief of Naval Air Reserve Training, Naval Air Station, Glenview, Illinois."

SOCIEDAD MEXICANA DE ALERGISTAS

In a letter dated March 29, Dr. Mario Salazar Mallen, of Mexico City, writes that a Sociedad Mexicana de Alergistas has been founded and has started its activities by giving a short course in allergy in Tampico, Mexico.

Doctor Salazar Mallen, who is president of this new society, states that one of the aims of the society is to maintain cordial relations with similar societies and asks that greetings be extended to the members of the American College of Allergists.

The College extends congratulations and welcome to the Sociedad Mexicana de Alergistas.

CUBAN SOCIETY OF DERMATOLOGY AND SYPHILOLOGY

For the year 1947, the following members have been elected to the Board of Directors of the Cuban Society of Dermatology and Syphilology: President, Dr. Jorge Pina; vice president, Dr. Pastor Fariñas; secretary, Dr. Guillermo González Peris; vice secretary, Dr. Luis Rodríguez Plasencia; treasurer, Dr. Federico Ordetz; and vice treasurer, Dr. Carlos Castaneda.

* * *

Miss Julia Garcia Games has opened an office in Santiago de Chile, for the purpose of supplying "rapid and correct information" on literary and scientific publications which appear in Latin America.

At the present time, Miss Garcia Games can supply any editorial which is published in Argentina, Uruguay, and Chile. She expects soon to include Peru, Bolivia, and the other countries in South America in this list. She will also furnish catalogs listing the literature of the following fields: poetry, stories, novels, theatre, art, history, law, social sciences, pedagogy, et cetera.

Orders will be taken care of by regular mail or airmail, as desired, and the charge will be figured accordingly.

Inquiries should be addressed to Miss Julia Garcia Games, Casilla 1091, Santiago de Chile, Chile.

* * *

Dr. James Eugene Stroh of Seattle, Washington, has received an appointment as Clinical Professor of Medicine at the University of Washington. Doctor Stroh will maintain his status of Chief of the Allergy Department at the King County Hospital.

* * *

Correction

A news item in the November-December issue of the ANNALS contained a list of countries in which the national allergy societies officially had become members of the International Association of Allergists. Through error, Denmark was included in this list.

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